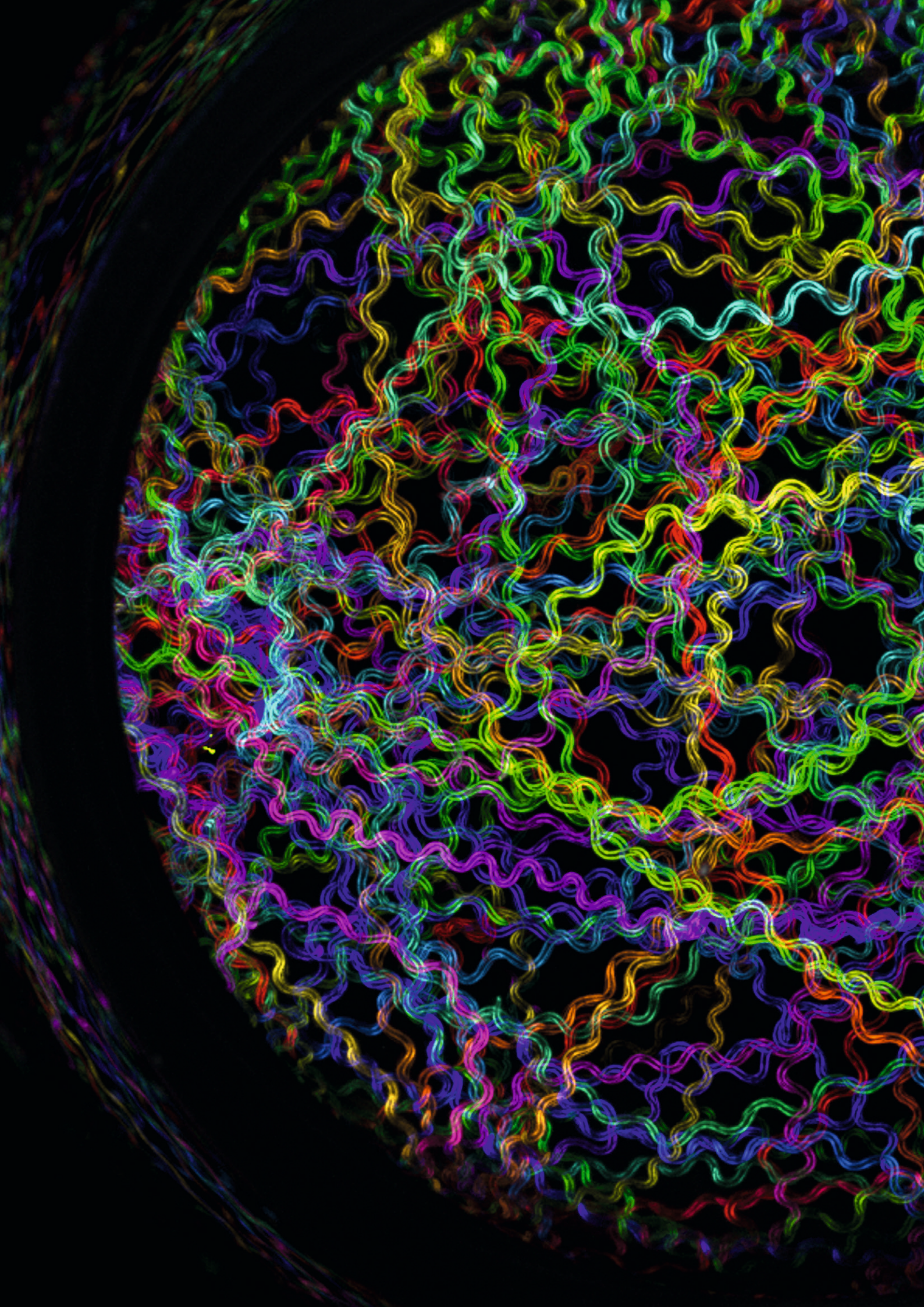
imb
Institute of
Molecular Biology

2025
ANNUAL REPORT



ANNUAL REPORT 2025

Welcome to IMB's 2025 Annual Report!

It is a pleasure to share the accomplishments of our researchers with you. Highlights from this year include our new recruits, top publications and collaborative events in ageing research.

STAFF CHANGES

At IMB, we pride ourselves on attracting top scientists from all over the world. In 2025, the institute grew to 307 staff and students, with 53 countries represented. We are delighted to announce two new group leaders, who will join us in 2026:

- Laura Lorenzo-Orts, from the Research Institute of Molecular Pathology (IMP) in Vienna, will explore how dormant maternal mRNAs are activated, translated and degraded in the early zebrafish embryo. She will also identify novel complexes involved in translating or storing mRNAs.

- Ulrich Hohmann comes to us from the Institute of Molecular Biotechnology (IMBA) and IMP in Vienna. He will investigate the regulation of mRNA nuclear export. Ulrich is working to find out how mRNA is hijacked in the germline for processing unusual RNAs (e.g. piRNA precursors), as well as how viruses rewire their host's mRNA export mechanisms to replicate.

Our International PhD Programme (IPP) recruited 30 new PhD students in 2025, bringing the total number of IPP students across IMB, Mainz University and the University Medical Center to 202.

As we welcome our new recruits, we must also bid farewell to departing members. We celebrated 35 successful PhD defences in the IPP this year. Claudia Keller Valsecchi, who was a group leader at IMB for almost 5 years, obtained an assistant professorship at the University of Basel in Switzerland and left in July. We are extremely proud of Claudia and all our alumni and wish them continued success for the next step of their careers.

On a sombre note, we are saddened by the loss of Nard Kubben, one of our group leaders, who passed away unexpectedly in September. Nard was a thoughtful scientist, a dedicated mentor, and a cherished colleague and friend to many. He will be deeply missed by the entire IMB community.

NEW PUBLICATIONS

IMB's scientific output remained strong in 2025, with 121 papers published in leading journals such as *Nature Communications*, *The EMBO Journal*, and *Genes & Development*. This year's highlights include:

- The Roukos lab's *Nature Protocols* paper, which describes a high-throughput method called BreakTag. This can be used to assess the location and structure of DNA double-strand breaks across the genome, providing essential information for improving the precision and predictability of CRISPR-Cas9 genome editing tools.

- The Stelzl and Dormann labs' paper in *Nature Communications*, in which they use coarse-grained simulations to identify factors that determine how TDP-43 is phosphorylated by CK1δ. They also show how phosphorylation might help dissolve TDP-43 condensates and reduce aggregation in neurodegenerative disease.

- The Lemke and Wittmann groups' paper in *Nature Communications*, in which they characterise conformational changes of the FG domain of the oncogenic transcription factor NUP98-HOXA9 as it forms condensates. This condensation behaviour is thought to be important for regulating gene expression and may explain how NUP98-HOXA9 activates genes in leukaemia.

- The Niehrs group's paper in *Nature Communications*, in which they developed a method called FIBo-seq to analyse the RNA modification 5-formylcytidine (f5C) in mammalian mRNA and show that it is unlikely to have an instructive function outside of tRNAs.

GRANTS & AWARDS

In 2025, IMB researchers received well over €7 million in extramural funding. Several group leaders also received prestigious honours and prizes: Claudia Keller Valsecchi was awarded the Friedrich Miescher Award 2025, Switzerland's highest distinction for young biochemists, and Christoph Cremer, an emeritus group leader, was awarded the David Glick Lectureship Award for his contributions to advancing the field of super-resolution microscopy. We warmly congratulate our colleagues on their achievements.

EVENTS AT IMB

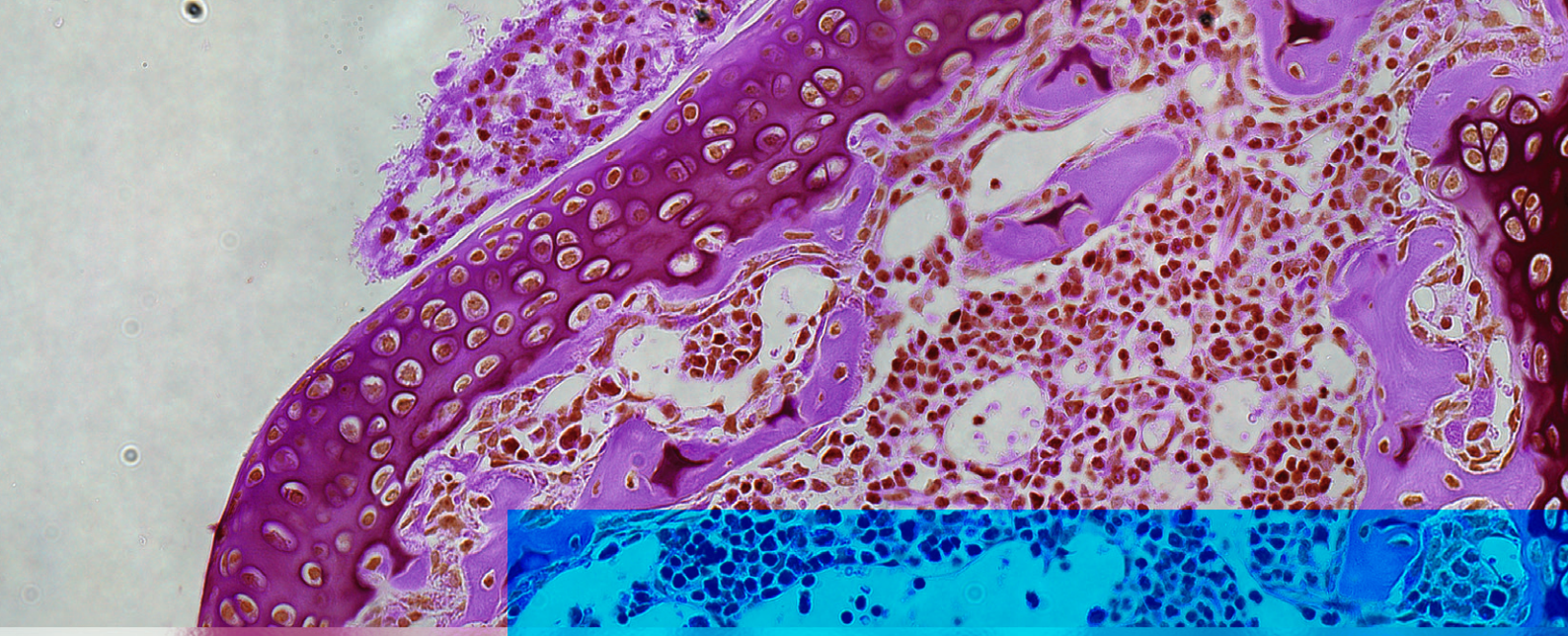
IMB had a busy schedule of scientific events in 2025. One highlight was the Cohorts for Healthy Ageing (CoAGE) kick-off meeting in June to mark the start of a new doctoral programme investigating the causes of age-related diseases using German cohort studies. Another was the second Centre for Healthy Ageing (CHA) Workshop in November, which brought together 93 leading scientists from the US, UK and Europe for an intense two-day session of talks, posters and discussions focusing on ageing research from different angles. We now look forward to the IMB/CRC 1361 conference in March 2026 on "The evil within: regulation and repair of endogenous DNA damage".

This year also saw the launch of our NextGen Training Programme, which replaces the previous International Summer School. The programme provides training in scientific and practical skills for Bachelor's and Master's students doing research placements at IMB, and was created to increase the institute's national and international visibility to junior researchers. We welcomed 40 students from 11 countries in the first year and will build on this momentum in the coming years.

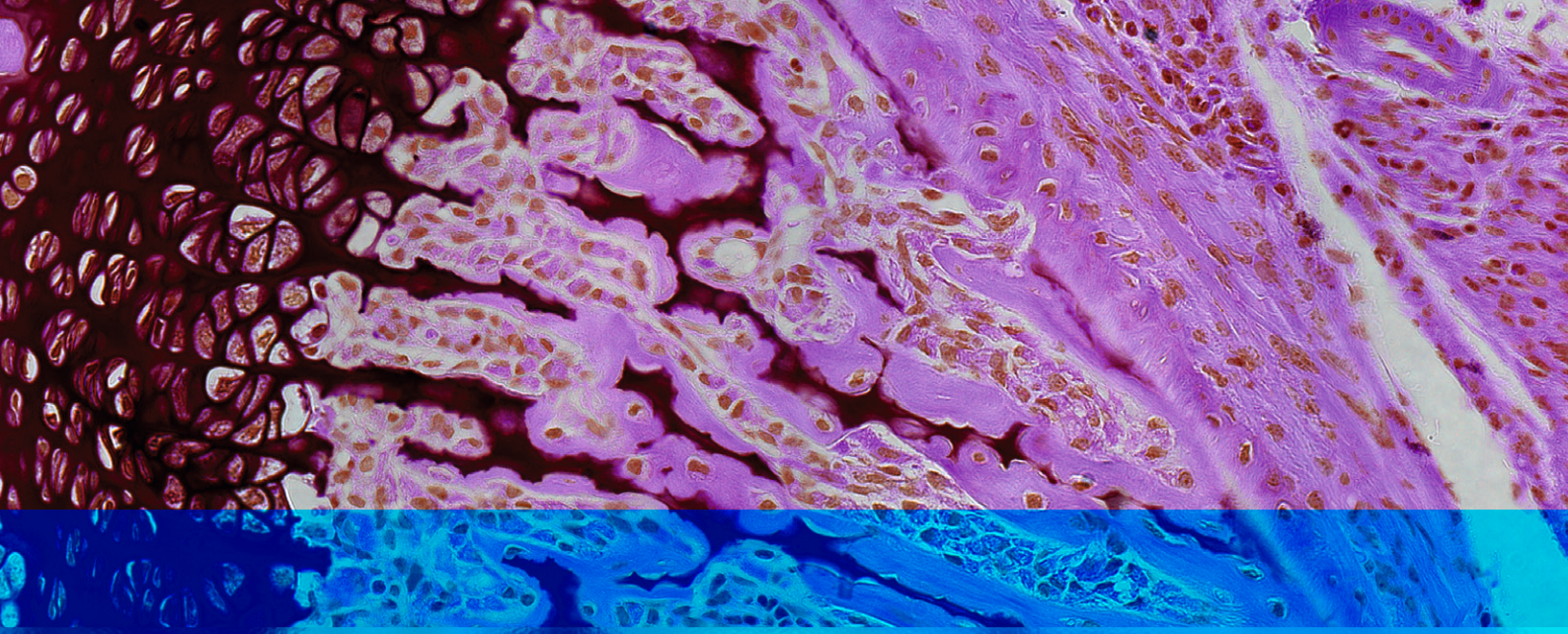
Our work at IMB would not be possible without the steadfast support and generous funding of the Boehringer Ingelheim Foundation and the State of Rhineland-Palatinate, for which we are deeply grateful. We equally appreciate our Scientific Advisory Board for their strategic guidance and constructive feedback as we continue to shape the future of the institute.

Finally, I would like to acknowledge the IMB community itself. Your passion, ingenuity and hard work are what set IMB apart as such an exceptional place for research and discovery.

Helle Ulrich
Executive Director



RESEARCH GROUPS



Roopesh **Anand**

> We elucidate the molecular mechanisms underlying critical steps of DNA repair pathways.

POSITIONS HELD

Since 2024 Group Leader, Institute of Molecular Biology (IMB), Mainz

2019 – 2024 Postdoc, The Francis Crick Institute, London

2016 – 2019 Postdoc, Institute for Research in Biomedicine (IRB), Bellinzona

EDUCATION

2016 PhD in Tumour Biology, University of Zurich

2011 MSc in Transfusion and Transplantation Sciences, University of Bristol

2009 BSc in Medical Laboratory Technology, Punjab Technical University

GROUP MEMBERS

Postdoc Lepakshi Ranjha

PhD Students Maxin Bakalo, Alicija Grzelak, Swaroopa Nakeeran

Technician Sanabel Chehab

DISCOVER MORE

OVERVIEW

Our lab primarily investigates the molecular mechanisms of DNA double-strand break (DSB) repair pathways. DSBs are highly toxic DNA lesions that, if repaired incorrectly, can lead to genomic instability and cancer development. Homologous recombination (HR) is one of the predominant pathways for DSB repair. HR is largely error-free, as it uses the sister chromatid as a template to guide accurate repair. It is a complex, multistep process involving critical stages such as homology search, DNA strand invasion, DNA synthesis, and DNA annealing. DSBs can also arise from persistent DNA:RNA hybrids, or R-loops—three-stranded structures formed during transcription. While most transcription-associated R-loops occur in *cis*, proteins such as RAD51AP1 can form R-loops in *trans* through their RNA-strand invasion activity. Remarkably, RAD51AP1-mediated R-loops not only facilitate HR-mediated DSB repair in transcriptionally active regions but also help maintain essential R-loop levels required for the survival of certain cancer cells. In our lab, we focus on elucidating the molecular mechanisms underlying critical steps of HR and its related pathways, and on determining how RAD51AP1 mechanistically forms R-loops in normal and cancer cells. To achieve these goals, we combine biochemical reconstitution with purified proteins, ensemble kinetics, and single-molecule imaging approaches.

RESEARCH HIGHLIGHTS

The mechanistic function of the DNA helicase HELQ in genomic stability maintenance

DNA helicases play a crucial role in DNA double-strand break (DSB) repair, particularly during homologous recombination (HR). HELQ is a 3′-to-5′ DNA helicase that functions in multiple DSB repair pathways, including HR. HELQ-deficient cells are hypersensitive to genotoxic agents, and mice lacking HELQ are more prone to tumour development, indicating its tumour suppressor function. We previously identified that HELQ also possesses robust DNA strand annealing activity and discovered its novel functions in alternative

DSB repair pathways. These discoveries have expanded the scope of HELQ's cellular functions in maintaining genomic stability. However, it remains unclear how HELQ utilises its dual enzymatic activities to exert its DSB repair functions at a mechanistic level. Recently, we found that the N- and C-terminal domains of HELQ differentially regulate its activities; the N-terminal domain is autoinhibitory, while the C-terminal domain is essential for HELQ's functions (Figure 1A-C). Using biochemical and cellular approaches, we aim to elucidate HELQ's mechanism of action in various DSB repair pathways to define its role in maintaining genomic stability and preventing cancer development.

Determining the molecular mechanism of R-loop formation by RAD51AP1

R-loops are three-stranded DNA:RNA hybrid structures in which RNA is annealed to one strand of the DNA duplex, displacing the other DNA strand. Persistent R-loops impede replication fork progression and can cause DSBs through transcription-replication collisions. Notably, R-loops are elevated in many cancers and can drive tumorigenesis. Alternative lengthening of telomeres (ALT) is a recombination-mediated process utilised by 10-15% of all cancers to maintain telomere length and avoid cell death. ALT cancer cells require sustained replication stress for telomere extension, and dynamic R-loop levels at telomeres induce the optimal stress for ALT to occur.

RAD51AP1 is a pro-HR factor that is upregulated in many cancers, and its loss results in hypersensitivity to genotoxic agents. It is essential for ALT cells due to its ability to generate R-loops in *trans* at telomeres. RAD51AP1 not only helps maintain critical telomeric R-loop levels but also indirectly promotes DNA strand invasion at these sites to facilitate efficient recombination. Similarly, during HR, when DSBs occur in actively transcribed regions, RAD51AP1 utilises local RNA transcripts to create R-loops in the donor DNA, promoting efficient strand invasion and D-loop formation through transient duplex opening. The resulting structure, in which both an R-loop and D-loop coexist on the same duplex, is known as a DR-loop.

The multifaceted roles of RAD51AP1 in DSB repair and ALT are only beginning to be understood. This project will define the mechanistic basis of RAD51AP1's R-loop formation activity *in vitro*. Using bulk biochemistry and single-molecule imaging techniques, we will elucidate the steps of R-loop formation, its transition to a D-loop (the DR-loop switch), and the subsequent initiation of DNA synthesis.

FUTURE DIRECTIONS

Error-free homologous recombination (HR) is crucial for maintaining genomic integrity and preventing cancer. Our goal is to delineate the critical steps of HR and its related pathways by elucidating the functions of the key repair proteins HELQ and RAD51AP1. The direct role of RAD51AP1 in ALT-based cancers is clinically significant, as it may reveal vulnerabilities for specifically targeting ALT-positive cancer cells.

To advance this, we will generate new separation-of-function mutants of HELQ to determine its physiological roles in cellular models and dissect the individual contributions of its DNA unwinding and annealing activities to DSB repair. In parallel, we will biochemically characterise the mechanism of R-loop formation by RAD51AP1 at both telomeric and non-telomeric DNA. We will also study the dynamics of the R-loop to D-loop transition (the DR-loop switch) to better understand its role in HR and the maintenance of telomeres in ALT cancers.

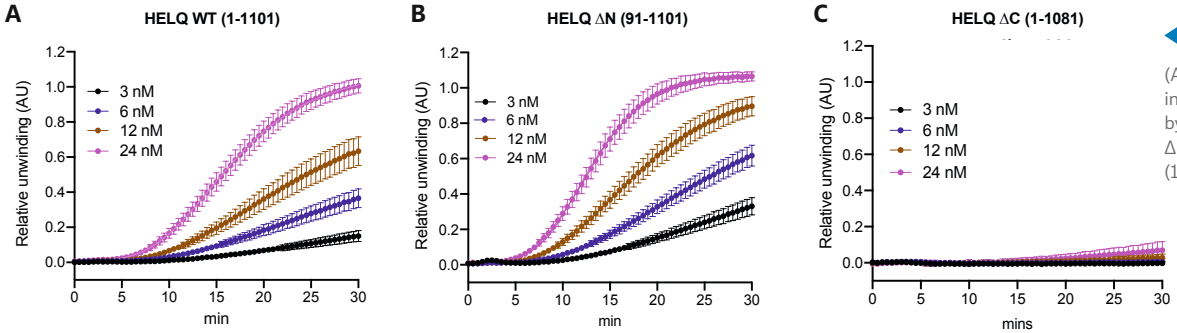


Figure 1

(A-C) Relative DNA unwinding of 3′ overhang substrate by HELQ WT (1-1101), HELQ ΔN (91-1101) and HELQ ΔC (1-1080) mutants.

SELECTED PUBLICATIONS

Belan O, Greenhough L, Kuhlen L, Anand R, Kaczmarczyk A, Gruszka DT, Yardimci H, Zhang X, Rueda DS, West SC and Boulton SJ (2023) Visualization of direct and diffusion-assisted RAD51 nucleation by full-length human BRCA2 protein. *Mol Cell*, 83:2925-2940.e8

Fleury H, MacEachern MK, Stiefel CM, Anand R, Sempeck C, Nebenfuehr B, Maurer-Alcalá K, Ball K, Proctor B, Belan O, Taylor E, Ortega R, Dodd B, Weatherly L, Dansoko D, Leung JW, Boulton SJ and Arnoult N (2023) The APE2 nuclease is essential for DNA double-strand break repair by microhomology-mediated end joining. *Mol Cell*, 83:1429-1445.e8

Anand R*, Buechelmaier E*, Belan O, Newton M, Vancevska A, Kaczmarczyk A, Takaki T, Rueda DS, Powell SN and Boulton SJ (2022) HELQ is a dual-function DSB repair enzyme modulated by RPA and RAD51. *Nature*, 601:268-273

*indicates joint contribution

Peter **Baumann**

> We explore telomere biology disorders & the 'ageing' of genomes in evolution.

POSITIONS HELD

Since 2023	Founding Director, Institute for Quantitative and Computational Biosciences (IQCB)
Since 2021	Director, Centre for Healthy Ageing (CHA), Mainz
Since 2018	Adjunct Director, Institute of Molecular Biology (IMB), Mainz
Since 2017	Alexander von Humboldt Professor, Johannes Gutenberg University Mainz (JGU)
2013 – 2019	Professor, Kansas University Medical Center
2013 – 2018	Investigator, Howard Hughes Medical Institute, Kansas City
2013 – 2018	Priscilla Wood-Neaves Endowed Chair in the Biomedical Sciences, Stowers Institute for Medical Research, Kansas City
2013 – 2018	Investigator, Stowers Institute for Medical Research, Kansas City
2009 – 2013	Early Career Scientist, Howard Hughes Medical Institute, Kansas City
2009 – 2013	Associate Professor, Kansas University Medical Center
2009 – 2012	Associate Investigator, Stowers Institute for Medical Research, Kansas City
2004 – 2009	Assistant Professor, Kansas University Medical Center
2002 – 2008	Assistant Investigator, Stowers Institute for Medical Research, Kansas City
1998 – 2002	Research Associate, University of Colorado, Boulder

EDUCATION

1998	PhD in Biochemistry, University College London
1994	MPhil, University of Cambridge

GROUP MEMBERS

Postdocs Nadine Bobon, Nathaniel Deimler, Lars Erichsen, Zoe Gill, David Ho, Lili Pan, Valentine Patterson
PhD Students Wafa Abuhashem, Yu-Chia Ku, Pauline Ott, Jayaprakash Srinivasan
Technicians Yvonne Hammer, Elisa Thomas
Animal Caretaker Martin Fahr
Personal Assistant Thomas Faust

DISCOVER MORE

OVERVIEW

Telomere shortening is one of the primary hallmarks of ageing, with direct impacts on genome stability and tissue renewal. Genetic defects in the machinery that maintains the integrity of chromosome ends are causative for a group of premature ageing diseases referred to as telomere biology disorders (TBD). At the cellular level, TBDs are characterised by premature loss of replicative capacity, stem cell exhaustion and the accumulation of senescent cells in tissues. Phenotypically, TBDs are characterised by many symptoms that are also associated with the normal ageing process, including greying hair, type II diabetes, osteoporosis, fibrosis and immune ageing. Studying the mutations that underlie TBDs thus provides valuable insights into the molecular and cellular changes that lead to functional decline as we grow older. Our group studies two key aspects of telomere maintenance: 1) the biogenesis, regulation and recruitment of the enzyme telomerase, and 2) the mechanistic basis of chromosome capping. We are guided by the conviction that understanding telomerase biogenesis will lead to the identification of compounds that modulate telomerase activity. Telomerase inhibitors can have therapeutic value for limiting tumour cell proliferation, and compounds that stimulate telomerase could boost the proliferation of desired cell populations, for example in the immune system. The latter could not only help patients suffering from TBDs, but may also counteract manifestations of the normal ageing process. Careful targeting and regulation are critical to balance regenerative effects with the increased risk of carcinogenesis. To reach these goals, we employ computational, molecular and cell biological approaches and have built a network of collaborators to examine telomere dynamics in the contexts of immune senescence, frailty and ageing.

RESEARCH HIGHLIGHTS

Telomerase biogenesis and regulation

Progressive telomere shortening is intrinsically linked to cell division via the "end replication problem", and critically short telomeres trigger cellular senescence, which in turn prevents further proliferation

and telomere shortening. Enzymes that replenish telomeric DNA are a double-edged sword: on one hand, they extend the replicative lifespan of a cell population and are vital for tissue renewal, but on the other hand, replenishing telomeres permits the continued proliferation of malignant cells. Consequently, telomere addition is tightly controlled in many multicellular organisms, including humans. Important layers of control affect the biogenesis of telomerase, from transcription and RNA processing to complex assembly and recruitment to telomeres. Our group studies these processes in fission yeast and human cells. Based on earlier work in fission yeast, we recently identified important roles for LARP3, LARP7 and MePCE during the early stages of telomerase assembly.

In collaboration with the Human Genetics Department at the University Medical Center, we are studying mutations responsible for telomere biology disorders, including dyskeratosis congenita and idiopathic pulmonary fibrosis. Combining clinical with cell biological, biochemical and bioinformatic analysis, we recently characterised a new class of telomerase mutations that affects telomere maintenance in two ways: 1) by diminishing the activity and processivity of the enzyme, and 2) by incorporation of non-canonical repeat sequences that subsequently affect the activity of wild-type telomerase, even in descendants that have not inherited the causative mutation.

Although telomere length is frequently used as a biomarker in the context of ageing and stress and to predict various disease outcomes, measuring telomere length reliably and accurately has been mired by technical challenges. Classical approaches require fresh blood samples or suffer from issues of reproducibility and reagent availability. This has hampered the acquisition of reproducible and especially longitudinal datasets on telomere length dynamics. Third-generation sequencing technologies now promise to reshape the field by providing a low-cost, accurate and reliable method of determining telomere length (Figure 1). Over the past two years, our group has invested considerable resources in developing telomere enrichment and sequencing protocols, as well as base calling and analysis pipelines.

FUTURE DIRECTIONS

To gain a comprehensive understanding of human telomerase biogenesis, regulation and turnover, present studies are aimed at identifying additional factors and using biochemical and genetic means to elucidate their functions. Unravelling how telomerase is made and regulated has led us to several exciting questions: Can we modulate telomerase activity by manipulating RNA processing? Is increasing telomerase levels a genuine path toward treating premature ageing diseases? Does increased telomerase activity contribute to resilience and delay the onset of degenerative processes associated with normal ageing? Complementing these avenues of inquiry are projects to understand how chromosome end protection is accomplished across a naturally-occurring telomere length distribution and how different repair pathways engage denuded chromosome ends and contribute to genome instability.

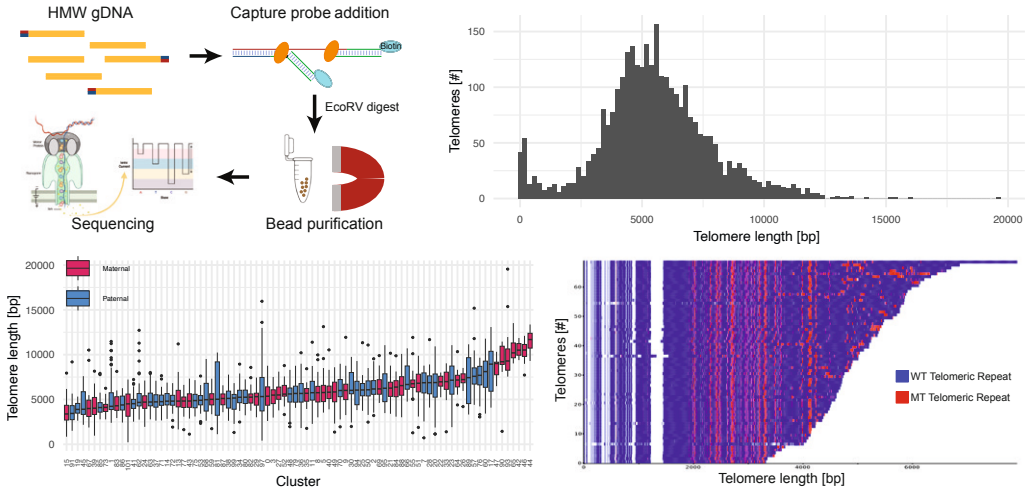


Figure 1

Long-read sequencing permits chromosome arm-specific analysis of telomere length and modification status, as well as the identification of non-canonical repeats. Telomeres are enriched from total genomic DNA and sequenced directly on Oxford Nanopore Technology flow cells. Bioinformatic analysis yields information on telomere length distribution and parent-of-origin- and chromosome arm-specific telomere length, as well as mutant telomeric repeat patterns.

SELECTED PUBLICATIONS

Ho DV*, Tormey D*, Odell A, Newton AA, Schnittker RR, Baumann DP, Neaves WB, Schroeder MR, Sigauke RF, Barley AJ and Baumann P (2024) Post-meiotic mechanism of facultative parthenogenesis in gonochoristic whiptail lizard species. *eLife*, 13:e97035

Pan L, Tormey D, Bobon N and Baumann P (2022) Rap1 prevents fusions between long telomeres in fission yeast. *EMBO J*, 41:e110458

Páez-Moscoso DJ, Ho DV, Pan L, Hildebrand K, Jensen KL, Levy MJ, Florens L and Baumann P (2022) A putative cap binding protein and the methyl phosphate capping enzyme Bin3/MePCE function in telomerase biogenesis. *Nat Commun*, 13:1067

*indicates joint contribution

Petra **Beli**

> We use quantitative proteomics to systematically identify proteome maintenance mechanisms.

POSITIONS HELD

Since 2020 Adjunct Director, Institute of Molecular Biology (IMB), Mainz

Professor of Quantitative Proteomics, Johannes Gutenberg University Mainz (JGU)

2013 – 2020 Emmy Noether Group Leader, Institute of Molecular Biology (IMB), Mainz

2010 – 2013 Postdoctoral Fellow, Novo Nordisk Foundation Center for Protein Research, University of Copenhagen

EDUCATION

2011 PhD in Biology, Goethe University Frankfurt

2007 MSc in Molecular Biology, University of Zagreb

GROUP MEMBERS

Staff Scientists Francesca Conte, Ivan Mikicic

Postdoc Aldwin Suryo Rahmanto

PhD Students Fatima Zahra Alkafri, Georges Blattner, Caio Almeida Batista De Oliveira, Christian Blum, Nadia da Silva Fernandes Lucas*, Lukas Graf, Rebecca Hobrecht*, Ekaterina Isaakova, Tim Preißendörfer, Eric Schmitt

Lab Manager
Katharina Elisabeth Lepp

Personal Assistant Ute Sideris

Student Assistants Felix Lorscheiter, Julia Isabet Zamora Interiano

*indicates joint PhD student

DISCOVER MORE

OVERVIEW

Human cells are exposed to stress induced by pollutants from the environment, as well as compounds generated during normal metabolism, such as reactive aldehydes. Genome maintenance is essential for the fidelity of gene expression, as well as the prevention of cancer and premature ageing phenotypes. Complementary to genome maintenance mechanisms, RNA and protein quality control pathways deal with stress-induced RNA and protein damage. The research in our group focuses on identifying and characterising proteins and signalling pathways that counteract genomic instability and the pathological effects of RNA and protein damage. We develop and employ quantitative mass spectrometry-based approaches to obtain systematic insights into the proteins and signalling pathways involved in these processes.

RESEARCH HIGHLIGHTS

A complex network of proteins and signalling pathways ensures genome and proteome maintenance in response to external stressors and by-products of cellular metabolism, as well as DNA replication and transcription. Reactive aldehydes are produced by normal cellular metabolism or after alcohol consumption, and they accumulate in human tissues if aldehyde clearance mechanisms are impaired. Their toxicity has been attributed to the damage they cause to genomic DNA and the subsequent inhibition of transcription and replication. However, whether interference with other cellular processes contributes to aldehyde toxicity has not been investigated. We demonstrated that formaldehyde induces a specific type of RNA damage – RNA-protein crosslinks (RPCs) – that stalls the ribosome and inhibits translation in human cells. RPCs in messenger RNAs (mRNAs) are recognised by translating ribosomes and marked by heterotypic K6/K48-linked ubiquitylation catalysed by the RING-in-between-RING (RBR) E3 ligase RNF14. Ubiquitylation of RPCs results in recruitment of the ubiquitin- and ATP-dependent unfoldase VCP (also known as p97), which promotes RPC resolution. Our findings uncover an evolutionarily

conserved formaldehyde-induced stress response pathway that protects cells against RPC accumulation in the cytoplasm, and they suggest that RPCs contribute to the cellular and tissue toxicity of reactive aldehydes. Following up on our findings that reactive aldehydes induce RNA damage in the form of RPCs and ribotoxic stress, we performed a comparative phosphoproteomics screen to identify changes in cellular signalling in response to different types of DNA and RNA damage. This enabled us to distinguish stress-induced DNA or RNA damage signalling and identify potential new factors involved in the RNA damage response (RDR). We found that RNA damage-induced hyperphosphorylation occurs in intrinsically disordered regions and is enriched on proteins that localise to membraneless condensates.

FUTURE DIRECTIONS

We are interested in understanding transcription- and translation-coupled quality control mechanisms that maintain the fidelity of gene expression and protein synthesis. We will use quantitative mass spectrometry-based proteomics to investigate cellular responses to stresses that cause damage to DNA and RNA. Our studies will focus on components of the ubiquitin system that regulate cellular responses to stress by catalysing the modification of substrate proteins with different types of ubiquitin chains. We will characterise ubiquitin-based mechanisms and ubiquitin E3 ligases that protect human cells from the deleterious effects of transcriptional and translational stress.

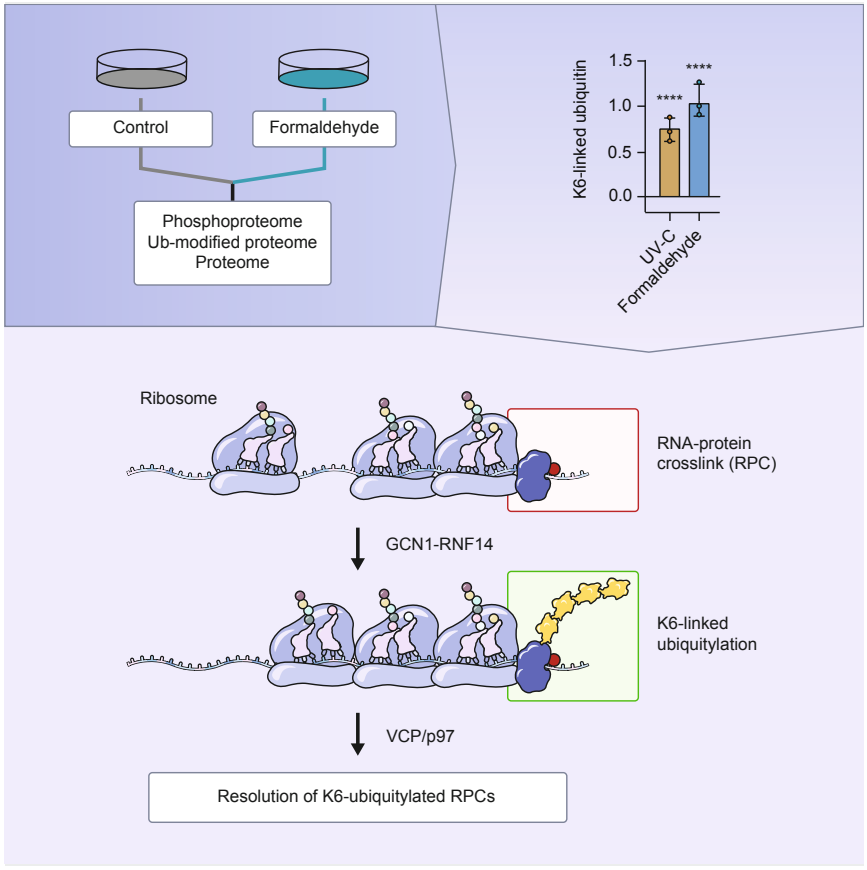


Figure 1

Systematic characterisation of the phosphoproteome and ubiquitin-modified proteome after formaldehyde exposure identified a new pathway for the resolution of RNA-protein crosslinks (RPCs). Ribosome stalling at the RPC induces the ribotoxic stress response mediated by ZAKα and K6-linked ubiquitylation on the RPC, which is dependent on GCN1 and the conserved E3 ligase RNF14.

SELECTED PUBLICATIONS

Longo GMC*, Sayols S*, Kotini AG, Heinen S, Möckel MM, Beli P and Roukos V (2025) Linking CRISPR-Cas9 double-strand break profiles to gene editing precision with BreakTag. *Nat Biotechnol*, 43:608-622

Suryo Rahmanto A*, Blum CJ*, Scalera C, Heidelberger JB, Mesitov M, Horn-Ghetko D, Gräf JF, Mikicic I, Hobrecht R, Orekhova A, Ostermaier M, Ebersberger S, Möckel MM, Krapoth N, Da Silva Fernandes N, Mizi A, Zhu Y, Chen JX, Choudhary C, Papantonis A, Ulrich HD, Schulman BA, König J and Beli P (2023) K6-linked ubiquitylation marks formaldehyde-induced RNA-protein crosslinks for resolution. *Mol Cell*, 83:4272-4289.e10

Mosler T, Conte F, Longo GMC, Mikicic I, Kreim N, Möckel MM, Petrosino G, Flach J, Barau J, Luke B, Roukos V and Beli P (2021) R-loop proximity proteomics identifies a role of DDX41 in transcription-associated genomic instability. *Nat Commun*, 12:7314

*indicates joint contribution

Dorothee **Dormann**

> We study how RNA-binding proteins aggregate in neurodegenerative diseases.

POSITIONS HELD

Since 2021 Adjunct Director, Institute of Molecular Biology (IMB), Mainz

Professor of Molecular Cell Biology, Johannes Gutenberg University Mainz (JGU)

2014 – 2021 Emmy Noether Group Leader, Biomedical Center, Ludwig Maximilian University (LMU), Munich

2007 – 2014 Postdoctoral Fellow, Adolf-Butenandt Institute, Ludwig Maximilian University (LMU), Munich

EDUCATION

2007 PhD, Rockefeller University, New York

2002 Diplom in Biochemistry, Eberhard Karl University of Tübingen

GROUP MEMBERS

Staff Scientists Nicole Belo Do Couto, Bernhard Lieb, Irene Yiallouros

Postdocs Saskia Hutten, Francesca Simonetti, Barbara Trifault, Federico Uliana

PhD Students Sebastian Gruber, Simone Mosna, Emre Pekbilir, Yongwon Suk, Sára Varga, Fatmanur Tiryaki, Yelyzaveta Zadorozhna

Lab Manager Nora Knabe

Research Assistant Thomas Schubert

Student Assistant Konrad Wiesler

Group Administrator Andrea Rautenberg

DISCOVER MORE

OVERVIEW

We seek to unravel the molecular basis of age-associated neurodegenerative diseases, in particular ALS (amyotrophic lateral sclerosis), FTD (frontotemporal dementia) and Alzheimer's disease. Existing therapies treat only the symptoms of disease and there are no therapies to slow down or stop disease progression. Our main objective is to obtain a molecular understanding of the mechanisms that drive these devastating disorders. We seek to unravel how RNA-binding proteins (RBPs), in particular TDP-43 and FUS, become mislocalised and aggregated, and how their dysregulation causes a decline in cellular function and eventually neurodegeneration. We previously showed that RBP mislocalisation and aggregation are intimately linked to 1) disturbed nuclear import, 2) aberrant condensation and molecular ageing processes and 3) altered post-translational modifications (PTMs). We therefore study how nuclear transport, condensation and PTMs of disease-linked RBPs are regulated, how they are misregulated in disease and how cellular proteostasis mechanisms prevent this. We are particularly interested in understanding the self-assembly behaviour of RBPs into different types of clusters and condensates, and how they relate to physiological function and disease. By understanding the molecular basis of these processes and learning how to tune them, we hope to inspire new therapeutic approaches to treat neurodegenerative diseases.

RESEARCH HIGHLIGHTS

In our research, we uncovered important proteostasis mechanisms that protect against RBP aggregation. Using *in vitro* reconstitution and cellular experiments, we showed that nuclear import receptors (importins) suppress phase separation and stress granule recruitment of FUS, TDP-43 and toxic repeat proteins (poly-GR and -PR) that arise in the most common inherited form of ALS and FTD. This suggests that elevating importin levels or enhancing the binding of importins to aggregation-prone proteins could be a strategy for treating protein aggregation disorders. Moreover, we found that

C-terminal TDP-43 phosphorylation, which occurs in ALS and FTD patients, reduces TDP-43 phase separation and aggregation, suggesting that TDP-43 phosphorylation may be a protective mechanism and may regulate TDP-43 condensation under physiological conditions. In support of this hypothesis, we recently found that TDP-43 phosphorylation is induced upon cellular stress, e.g. sodium arsenite treatment, and identified tau tubulin kinase 2 (TTBK2) as a key kinase regulating cytosolic TDP-43 condensation. Furthermore, we uncovered how the cellular degradation machineries (proteasome and autophagy) cooperate to clear cytosolically mislocalised TDP-43 and disease-associated C-terminal fragments (CTFs) of TDP-43. While the proteasome clears soluble TDP-43, the autophagy machinery, involving the autophagy receptors p62/SQSTM1 and NBR1, recognises and degrades TDP-43 condensates/aggregates with the help of ATP-dependent chaperones such as Hsp70, which are involved in fragmenting cytosolic TDP-43 condensates/aggregates.

Additionally, we investigated the interplay between TDP-43 and tau to understand the molecular basis of TDP-43/tau pathology in Alzheimer's disease (AD). We found that the tau protein directly interacts with TDP-43 and influences its condensation and aggregation behaviour *in vitro*. While tau promotes TDP-43 aggregation *in vitro*, TDP-43 suppresses the formation of tau fibrils and instead causes the formation of oligomeric tau and tau/TDP-43 species. In a biosensor cell culture assay specific for proteopathic tau seeds, these co-assemblies hinder tau seeding (Figure 1). In line with these findings, insoluble material extracted from AD patient brains with tau/TDP-43 co-aggregates exhibits reduced tau seeding compared to AD patient brains with tau aggregates only. In contrast, patient-derived extracts from AD patient brains with tau/TDP-43 co-aggregates are highly potent in seeding new TDP-43 aggregates in a TDP-43 reporter cell line. Our results suggest that direct interaction between TDP-43 and tau may suppress tau pathology while promoting TDP-43 pathology in AD patients.

FUTURE DIRECTIONS

As molecular self-assembly into clusters or condensates appears to be an important pathway towards RBP aggregation, we want to gain a comprehensive understanding of its drivers and regulators and discover its relevance for RBP function. Specifically, we plan to systematically decipher the intrinsic sequence features that drive the self-assembly and aggregation of TDP-43, and identify and study new regulators/modifiers of these processes. One focus will be on disease-linked TDP-43 phosphorylation and understanding how it is regulated in cells, whether it can dissolve TDP-43 aggregates and how it alters TDP-43's interactome and physiological functions. In addition, we will study how RBP self-assembly into nanosized clusters or micron-sized condensates governs their interactions with other proteins and how this influences their functions in gene regulation, e.g. alternative splicing, transcription or translation. Finally, we will study the molecular mechanisms of how disease-linked RBPs regulate R-loops and DNA damage repair and how damage-associated PTMs, such as ADP-ribosylation, regulate RBP condensation and dynamics at DNA damage repair foci.

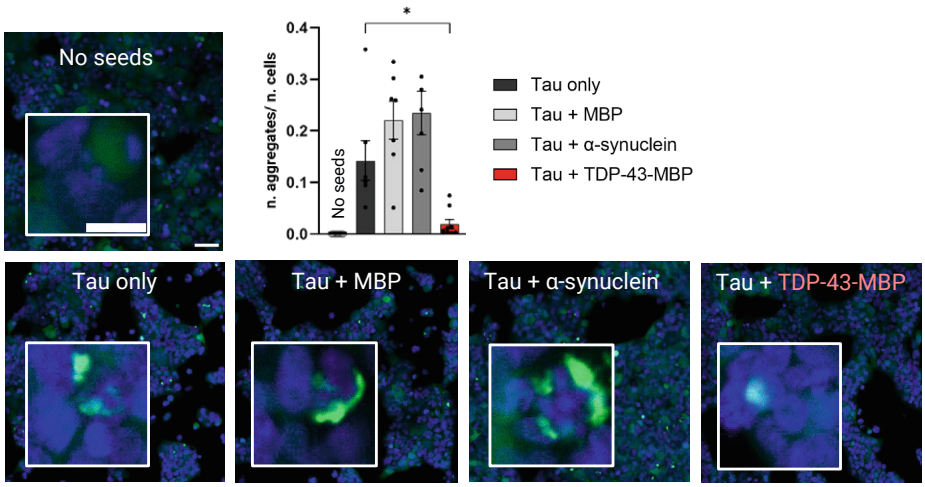


Figure 1

TDP-43 suppresses intracellular tau aggregation. Tau seeding assay in HEK293 GFP/YFP-TauRDP301S biosensor cells transfected with *in vitro*-generated tau assemblies or co-assemblies of tau with other proteins; representative confocal images of cytosolic tau aggregates (green) in tau biosensor cells are shown. Scale bar: 70 µm in overview and 20 µm in inset. Quantification shows the number of aggregates per cell (SEM of 5 biological replicates; $^{*}p$ = 0.0274 by one-way ANOVA Kruskal-Wallis test with Dunn's multiple comparison test).

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#indicates joint correspondence

Claudia **Keller Valsecchi**

> How gene dosage is balanced across the sexes reveals surprising flexibility in how life adapts.

POSITIONS HELD

Since 2025	Assistant Professor, Biozentrum, University of Basel, Switzerland
2020 – 2025	Group Leader, Institute of Molecular Biology (IMB), Mainz
2013 – 2020	Postdoc, Max Planck Institute of Immunobiology & Epigenetics, Freiburg
2012 – 2013	Postdoc, Friedrich Miescher Institute (FMI), Basel

EDUCATION

2012	PhD in Biochemistry, Friedrich Miescher Institute (FMI), Basel
2008	MSc in Molecular Biology, Friedrich Miescher Institute (FMI), Basel
2007	BSc in Molecular Biology, Biozentrum, University of Basel

GROUP MEMBERS

Senior Research Associate Maria Felicia Basilicata

Postdoc Qiaowei Pan

PhD Students José Hector Gibran Fritz Garcia*, Feyza Polat, Anna Szczepinska*, Frederic Zimmer

Student Assistants Joseph Andrew, Iona Bergerhoff, Annika Maria Fox

Lab Manager Anna Einsiedel

*indicates joint PhD students

DISCOVER MORE

OVERVIEW

Sexual reproduction facilitates the introduction of genetic diversity within a population. The diploid genetic state serves as a safeguarding mechanism by ensuring development when mutations occur in heterozygosity. Nevertheless, recent large-scale genome sequencing initiatives have uncovered an unexpectedly high number of human genes that exhibit intolerance to heterozygous loss-of-function mutations. Similarly, aneuploidies, characterised by the gain or loss of entire chromosomes, are a prominent cause of miscarriages and pregnancy failures. This suggests that maintaining a precisely two-fold gene dosage is of fundamental importance for the normal progression of organismal development.

Our approach is to understand these pathogenic deviations in gene dosage within the context of natural exceptions to the diploid genetic state. Notably, differentiated sex chromosomes, despite introducing heterozygosity for hundreds of genes, do not confer detrimental effects. This phenomenon can be attributed to dosage compensation (DC), a regulatory mechanism that corrects imbalances in X-chromosomal gene expression between males and females. We study this intriguing paradox surrounding natural gene dosage alterations and their potentially deleterious consequences. We investigate how cells effectively manage the interplay between advantageous elements, such as the evolution of sex chromosomes and novel genes, and adverse effects like developmental delays and malignancies.

RESEARCH HIGHLIGHTS

Dosage regulation in sex chromosomes

Sexual dimorphism is a prominent feature in the biology of various species, including the *Anopheles* mosquito, where only females require a blood meal for egg production. In comparative studies between *A. gambiae* and *D. melanogaster*, two related dipterans with similar X-chromosomal gene content, we unexpectedly found entirely different molecular mechanisms for DC. To identify the new mosquito pathway, we generated a sex-specific transcriptome atlas,

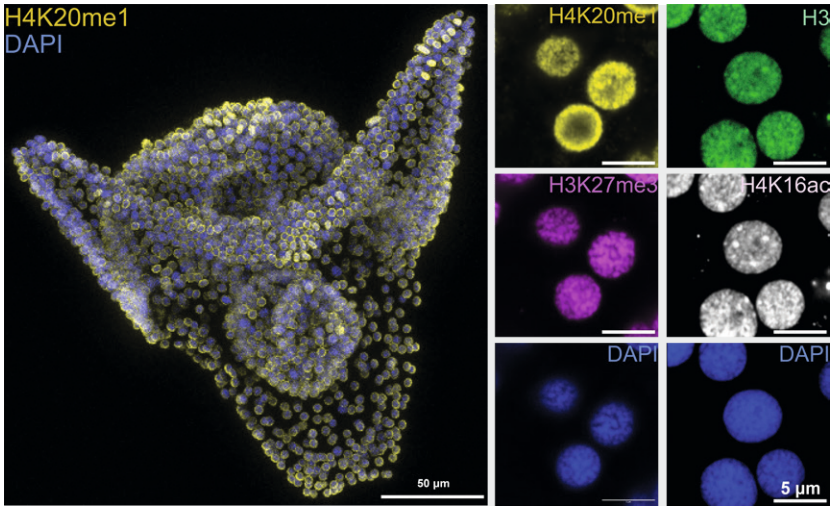
which revealed that DC is progressively established in embryogenesis. This dataset also uncovered *SOA*, an uncharacterised gene that we found to be sex-specifically spliced. SOA is a DNA-binding protein that binds X-chromosomal promoters. Expressing it is sufficient to induce global X chromosome upregulation. In collaboration with Eric Marois (University of Strasbourg), we generated SOA gain- and loss-of-function mutants, which display perturbed DC. Surprisingly, this is compatible with viability but causes a developmental delay, showing that DC is non-essential in mosquitos. Based on this exciting discovery, we now aim to understand X-to-autosome specificity, focusing on DNA elements that co-evolved with sex chromosome differentiation. We have established heterologous expression systems to analyse the SOA binding pattern in non-mosquito genomes, complemented by characterisations of SOA's DNA binding domain by biophysical methods. Secondly, to explore SOA's downstream regulatory actions, we identified its interaction partners by mass spectrometry and found that it binds to splicing factors and R-loop regulators. This research angle provides key insights into how genes are collectively recognised and regulated. It also highlights the importance of gene-dosage balance and may shed light on why copy number alterations have such detrimental consequences during human development but are apparently common in, e.g. the adult nervous system or in other species.

Plasticity of gene regulation in female-heterogametic species

Spatiotemporal environmental fluctuations, like those driven by climate change, pose challenges for species. Aquatic ectotherms such as crustaceans often exhibit environmentally influenced developmental plasticity and sex determination, with largely unknown molecular mechanisms. Our recent focus has been on *A. franciscana*, a crustacean with a ZW sex determination system and two alternative developmental pathways based on environmental conditions. We established *A. franciscana* rearing in our group to generate transcriptome data for both pathways and implemented ATAC-seq and CUT&Tag for sex-biased gene expression analysis. We found that upregulation of the female Z chromosome is mediated by H4K16 acetylation, and thus occurs in a similar fashion to *Drosophila*. In addition, *A. franciscana* males (ZZ) have longer lifespans than females (ZW). We hypothesise that this relates to a change in histone acetylation, Z chromosome regulation and transposon-triggered genomic instability. This research angle provides novel insights into environmental stressors, sex determination and phenotypic plasticity.

FUTURE DIRECTIONS

Our goal is to further characterise DC mediated by SOA. These findings could ultimately inform novel strategies for fighting infectious diseases such as malaria by vector control. In addition to our work with mosquitoes, we also investigate DC in various other non-model organisms. Our research focuses on several aspects, including tissue-specific differences, regulatory dynamics throughout an organism's lifespan and adaptability in response to environmental shifts. We aim to elucidate how H4K16ac DC is controlled in *A. franciscana* – by similar writer/eraser complexes to *Drosophila* or different ones? In parallel, we develop tools to comprehensively identify dosage-sensitive genes and cellular responses in mammals. We will also expand our work on the mammalian X chromosome and study the mechanisms of re-activation during development, as well as age-related chromosomal mosaicism during ageing.



▲ **Figure 1**

Immunofluorescence staining of a sea urchin embryo. Nuclei are visualised with DAPI (blue), and different histone modifications are labelled by immunostaining. The distinct nuclear localisation patterns of these epigenetic marks – peripheral or internal – suggest spatial compartmentalisation of chromatin states within the embryonic nuclei.

SELECTED PUBLICATIONS

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Zimmer F, Fox AM, Pan Q, Rühle F, Andersen P, Huylmans AK, Schwander T, Basilicata MF and Keller Valsecchi CI (2025) Convergent evolution of H4K16ac-mediated dosage compensation in the ZW species *Artemia franciscana*. *PLOS Genet*, 21:e1011895

Kalita AI, Marois E*, Kozielska M, Weissing FJ, JaouenE, Möckel MM, Rühle F, Butter F, Basilicata MF* and Keller Valsecchi CI* (2023) The sex-specific factor SOA controls dosage compensation in *Anopheles* mosquitos. *Nature*, 623:175–182

*indicates joint contribution

René **Ketting**

> We study how small non-coding RNAs regulate gene activity.

POSITIONS HELD

Since 2012	Scientific Director, Institute of Molecular Biology (IMB), Mainz
	Professor, Johannes Gutenberg University Mainz (JGU)
2010 – 2013	Professor of Epigenetics in Development, University of Utrecht
2005 – 2012	Group Leader, Hubrecht Institute, Utrecht
2000 – 2004	Postdoc, Hubrecht Institute, Utrecht
2000	Postdoc, Cold Spring Harbor Laboratories

EDUCATION

2000	PhD in Molecular Biology, Netherlands Cancer Institute, Amsterdam
1994	MSc in Chemistry, University of Leiden

GROUP MEMBERS

Staff Scientists Diego Páez Moscoso, Nadine Wittkopp

Postdocs Mezmur Belew, Qiaowei Pan, Joana Sofia Costa Pereirinha, Nadezda Podvalnaya, Ann-Sophie Seistrup, Shamitha Shamitha

PhD Students Mohd Aaquib, Fiona Carey, Sarah Hallstein, Ida Josefine Isolehto, Joao Marques, Joanna Michowicz, Lizaveta Pshanichnaya, Eva Richard

Research Technician Yasmin El Sherif

Technicians Svenja Hellmann, Yuliia Plishch

Student Assistants Celine Bitter, Katja Göbel, Teo Llazo, Viktoria Peter, René-Maurice Pfeifer, Nadine Spiegler

Animal Caretakers Daniela Albore, Stefanie Schlegel

Personal Assistant Jutta Karn

DISCOVER MORE

OVERVIEW

A major focus of my lab is gene regulation by small RNA molecules acting through RNAi-related pathways. Since their discovery at the start of the 21st century, various RNAi-related pathways have been identified. It is now evident that although all of these pathways depend on proteins from the Argonaute family, each pathway has its own unique characteristics and effects on gene expression. These can range from relatively minor effects on translation (in the case of miRNAs) to full-blown shutdown of loci at the transcriptional level (piRNAs). We focus on the mechanisms related to piRNA and siRNA biology, two species of small RNAs that are particularly abundant in and important for the germline. These pathways have a major role in maintaining genome integrity by controlling transposable element activity. In addition, we also study miRNAs in relation to germ cells. We use zebrafish and *C. elegans* as model systems to understand the molecular mechanisms governing these pathways and how they contribute to development. Questions such as how small RNA pathways distinguish transposable elements from regular genes, how these pathways are organised at a sub-cellular level and how small RNA populations can be inherited across generations are at the heart of our research.

RESEARCH HIGHLIGHTS

In 2025, we made good progress on a number of fronts. In one project, we are dissecting the evolutionary roots of the nematode piRNA biogenesis mechanism. Our experiments led us to identify a novel mechanism by which a specific class of mRNAs is stabilised, such that it can be stored in the oocytes for use during the early cell divisions of the embryo. The specific mRNA class affected by this mechanism is that of the replication-dependent histone mRNAs. These transcripts are needed during cell division only, and they are normally tightly regulated, such that they accumulate only during the S-phase of the cell cycle, in which new histone proteins are required to shape the chromatin. However, these transcripts are also needed during early embryonic cell division, at which stages no

transcription takes place yet. We found that the protein complex we previously identified and found to stabilise small RNA precursors, notably piRNA precursors, also stabilises these maternally provided histone mRNAs. It does so starting at the pachytene stage of meiosis, lasting until oogenesis. In fact, this seems to be its ancestral function, implying that its role in piRNA biogenesis reflects an adapted function. The two functions are specified by two specific effector proteins, one of which is required for piRNA precursor stabilisation while the other only acts in histone mRNA stabilisation. In this work, we also identified new proteins that regulate histone mRNA and protein stability, and found evidence for transcription outside S-phase for these histone genes.

In our second main model system, the zebrafish, we have gained interesting insights into how a microRNA affects sex determination. We have been able to firmly establish that miR-214 has a strong effect on sex determination, but that the long non-coding RNA (lncRNA) in which it is embedded affects this process in a manner independent of miR-214. Our results are consistent with a role for miR-214 in controlling a gene named *gsdf*, combined with additional sex-determining activities from the lncRNA. This creates a complex sex-determination network rather than a simple linear genetic pathway. Further projects in this model system address how the germ cells are formed and function. More specifically, two lines of research are being pursued here. First, we address how a structure named germ plasm is formed. Germ plasm is a form of germ granules present in the early embryo and contains many RNAs and proteins needed to make the germ cells. Second, we study a de-ubiquitinating (DUB) enzyme that appears to play a role in oocyte growth and maturation. Here, the results suggest that the DUB enzyme is needed to stabilise RNA-protein complexes that are critical for oocyte development and germ cell formation in the embryo.

FUTURE DIRECTIONS

Future work will continue to mechanistically unravel the molecular pathways that are steered by small RNA molecules. One aim will be to further focus on the role of biomolecular condensates in small RNA-mediated gene silencing. Such condensates are well known to be required, but their exact functions are unclear. These studies also aim to provide a more generally applicable framework for the roles of condensates in cell biology. We will also continue to delineate how small RNAs are processed and loaded into Argonaute proteins. Finally, we are zooming into the interfaces between small RNA biology and other aspects of gene regulation. Using genetic screens and immunoprecipitation approaches, we are identifying novel factors and then implementing these into our current models of gene regulatory mechanisms.

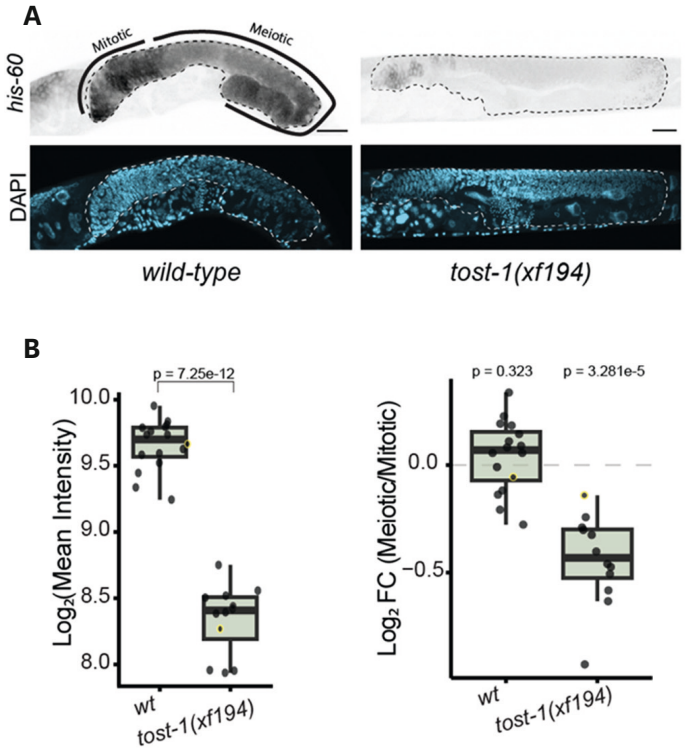

Figure 1

A) A single molecule FISH experiment visualising histone mRNA expression in the gonad of *C. elegans* (outlined by the dashed line). Top images: smFISH signal; bottom images: DAPI. The left panel represents a wild-type animal, which shows histone mRNA expression throughout the gonad, but with clear enrichment of signal at the start (mitotic zone) and the end (meiotic zone) of the gonad. The right two images show a *tost-1* mutant, in which the histone mRNA stabilising complex is dysfunctional. Here, expression after the mitotic zone basically disappears. The two graphs reflect quantification of similar images. B) Left graph: comparison of overall signal intensity over the entire gonads. Right graph: comparison of signal intensities in the mitotic versus the meiotic zones. The latter shows that *tost-1* mutants especially lose expression in the meiotic zone.

SELECTED PUBLICATIONS

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*indicates joint contribution, #indicates joint correspondence

Anton **Khmelinskii**

> How do cells keep their proteomes functional & balanced?

POSITIONS HELD

Since 2018	Group Leader, Institute of Molecular Biology (IMB), Mainz
2013	Visiting Scientist, Donnelly Centre for Cellular & Biomolecular Research, University of Toronto
2011 – 2017	Postdoc, Center for Molecular Biology (ZMBH), University of Heidelberg
2011 – 2016	Visiting Scientist, European Molecular Biology Laboratory (EMBL), Heidelberg
2010 – 2011	Postdoc, European Molecular Biology Laboratory (EMBL), Heidelberg

EDUCATION

2010	PhD in Biology, University of Heidelberg
2005	MSc in Biochemistry, University of Lisbon

GROUP MEMBERS

PhD Students Tatiana Aksinina, Maurice Bouchain, Cécile Debarnot, Eduardo Gameiro*, Joep Lurvink*, Christian Ochs

Lab Manager Anke Salzer

Research Assistant Elena Ivanova

Master's Student Johanna Bucka

Student Assistant Markus Zischewski

*indicates joint PhD student

DISCOVER MORE

OVERVIEW

The integrity of the proteome is maintained by a complex network that controls the synthesis, folding, transport and degradation of proteins. Numerous quality control systems operate throughout the protein life cycle to reduce mistakes or remove abnormal proteins, thus contributing to proteostasis. Selective protein degradation by the ubiquitin-proteasome system (UPS) plays a key role in proteome turnover and quality control. When degradation is not possible, abnormal proteins can eventually be removed via asymmetric partitioning during cell division. Despite the activity of such systems, proteostasis declines with ageing and in numerous diseases, resulting in the accumulation of abnormal proteins and loss of cell functionality. Working in yeast and human cells, we aim to systematically examine how cells deal with different types of abnormal proteins. We use genetic and proteomic approaches that exploit fluorescent timers to identify UPS substrates and explore the functions of this system in replicative ageing and genome stability. Our goals are to understand the coordination between protein biogenesis and quality control, decipher how abnormal proteins are recognised and elucidate how cells adapt to challenges in proteostasis.

RESEARCH HIGHLIGHTS

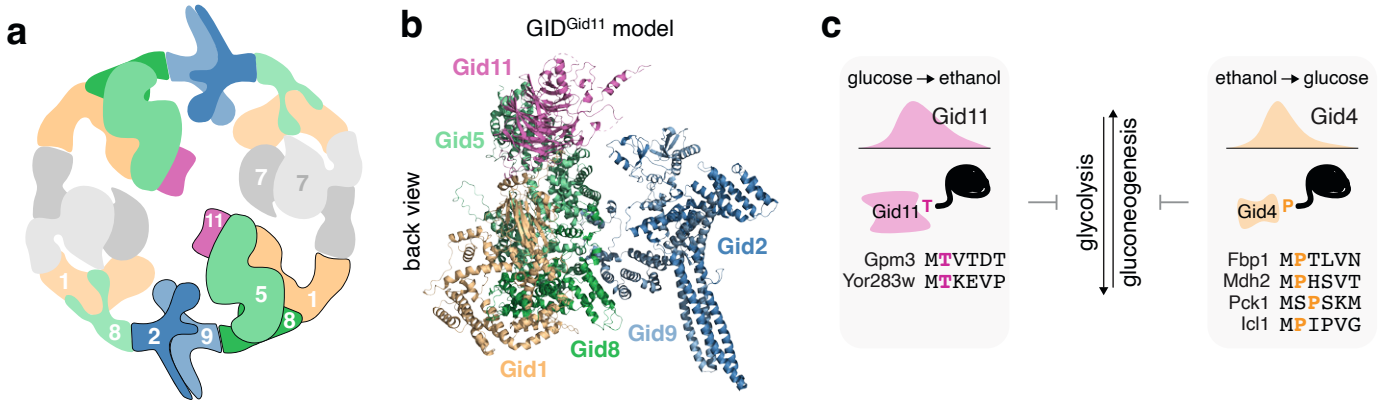
Selective protein degradation is involved in most cellular processes and contributes to proteome homeostasis through the removal of unnecessary or abnormal proteins. Despite the central role of the UPS in selective protein degradation and its association with various diseases and ageing, the functions of many UPS components are unclear and the substrate specificities of ubiquitin ligases (E3s) and deubiquitinating enzymes are not well defined. To address this gap, we previously completed a large-scale effort towards the first comprehensive characterisation of the UPS in a model organism, the budding yeast *Saccharomyces cerevisiae*. Using a colony-based proteomic assay with fluorescent timers, we examined how inactivation of individual UPS components affects proteome abundance

and turnover. This yielded a rich resource for studies of the UPS, revealing new substrates, functions and relationships between UPS components.

We exploited this unique dataset to gain insights into the functions of an understudied ubiquitin ligase called GID/CTLH, which has been implicated in metabolic regulation, cell proliferation, embryonic development and cell differentiation, with links to cancers and neurodevelopmental disorders. This led us to the discovery of a potential substrate receptor subunit, Gid11. We have now established Gid11 as a *bona fide* GID substrate receptor and characterised the regulation, specificity and functions of the GID-Gid11 complex (Kong *et al.*, 2025, *bioRxiv*; Figure 1). We found that upon its expression during the switch from glucose to ethanol as a carbon source, Gid11 associates with the core GID complex, likely forming a large ring assembly. Through systematic mutagenesis, we identified a negatively charged pocket on Gid11 that binds substrates carrying N-terminal degrons starting with threonine and defined the Thr/N-degron motif. Such Thr/N-degrons are exposed upon co-translational removal of the initiator methionine, while escaping N-terminal acetylation. Finally, we could show that during the switch to ethanol, GID-Gid11 targets degradation factors linked to glycolysis, opposing the established role of GID in the degradation of gluconeogenic enzymes during the reverse switch from ethanol to glucose (Figure 1). This appears to be the first example of such bidirectional control by a ubiquitin ligase.

FUTURE DIRECTIONS

Our work on the GID-Gid11 complex opened a number of exciting research directions. With genetic, biochemical and structural modelling approaches, we are examining alternative modes of substrate recognition by Gid11. Moreover, we are eager to identify further GID substrate receptors and analyse the conservation of GID specificities and functions across evolution.



▲ **Figure 1**

Bidirectional control of a metabolic transition by the GID ubiquitin ligase.
A) Cartoon representation of the GID-Gid11 complex. B) Validated Alphafold model of the core GID-Gid11 assembly. C) Model of the bidirectional switch between glucose and ethanol as carbon sources by conditional expression of two substrate receptors, Gid4 and Gid11. Their substrates and specificity determinants are indicated.

SELECTED PUBLICATIONS

Gameiro E*, Juárez-Núñez KA*, Fung JJ, Shankar S, Luke B° and Khmelinskii A° (2025) Genome-wide conditional degron libraries for functional genomics. *J Cell Biol*, 224:e202409007

Kong KYE*#, Shankar S*, Rühle F and Khmelinskii A# (2023) Orphan quality control by an SCF ubiquitin ligase directed to pervasive C-degrons. *Nat Commun*, 14:8363

Kong KYE*, Fischer B*, Meurer M*, Kats I, Li Z, Rühle F, Barry JD, Kirrmaier D, Chevyreva V, San Luis BJ, Costanzo M, Huber W, Andrews BJ, Boone C, Knop M# and Khmelinskii A# (2021) Timer-based proteomic profiling of the ubiquitin-proteasome system reveals a substrate receptor of the GID ubiquitin ligase. *Mol Cell*, 81:2460–2476

* indicates joint contribution, # indicates joint correspondence, ° indicates joint senior authorship

Nard **Kubben**

> Our research aims to discover therapeutic targets that improve healthspan.

POSITIONS HELD

2021 – 2025 Group Leader, Institute of Molecular Biology (IMB), Mainz

2015 – 2019 NIH Research Fellow, National Cancer Institute, NIH, Bethesda

2011 – 2015 NIH Postdoctoral Fellow, National Cancer Institute, NIH, Bethesda

EDUCATION

2004 – 2010 PhD in Molecular Biology, Maastricht University

2001 – 2004 MSc in Biological Health Sciences, Maastricht University

2000 – 2001 BSc in Health Sciences, Maastricht University

GROUP MEMBERS

PhD Students Luisa Hastenplug, Lukas Mann, Felix van der Walt

Master's Students Suna Aydinli, Jonathan Kraft

Bachelor's Student Fiona Hauschulte

Nard Kubben served as a Group Leader until his sudden passing in September 2025. These pages honor his dedication and the work he completed during the reporting period.

OVERVIEW

Ageing is a prime pathological component of most prevalent diseases. At the cellular level, it is characterised by various hallmarks, including epigenetic alterations, genomic instability and loss of protein homeostasis, all of which contribute to an organism-wide decline in function. Unfortunately, our current knowledge of the molecular pathways that drive cellular ageing and the formation of ageing hallmarks is severely limited. We focus on uncovering fundamental biological mechanisms of ageing that can be manipulated to slow down the progression of ageing-related diseases, including the rare and lethal premature ageing disease Hutchinson-Gilford Progeria Syndrome (HGPS). Our group employs unbiased genomics, proteomics and high-throughput microscopy-based screening to 1) identify novel pathways that slow down the onset of cellular ageing, 2) investigate cellular pathways that help reverse ageing defects that have already formed, and 3) validate the therapeutic potential of identified ageing mechanisms across various model systems of ageing-related diseases. The overarching goal of our research is to uncover fundamental biological mechanisms of ageing that can help improve human healthspan.

RESEARCH HIGHLIGHTS

A novel model system to identify drivers of ageing

One of the major challenges in ageing research is that ageing manifests as a slow build-up of relatively low percentages of aged cells in our bodies. Molecular techniques that directly compare young and aged biological tissue samples therefore have the disadvantage of only detecting the most robust ageing-correlated changes, many of which turn out to be a consequence rather than a cause of ageing. As such, it is key to establish a technical approach that excludes these passive bystander effects and focuses directly on identifying the mechanisms that actively drive ageing. We have therefore established an HGPS-based system to functionally screen for events that drive ageing. HGPS is predominantly caused by a silent mutation in the *LMNA* gene, which encodes the nuclear

lamina-localised protein lamin A, a key organiser of the mammalian nucleus. The mutation in HGPS results in the accumulation of an alternatively spliced lamin A mutant, termed progerin. A more modest accumulation of progerin also occurs during physiological ageing, suggesting that HGPS and physiological ageing have a common mechanistic basis. Unfortunately, the mechanisms by which progerin exerts its dominant negative effects remain largely unknown. We generated a cellular system in which we can inducibly express progerin and study the formation of many cellular ageing defects within a time frame of only four days, using a semi-automated high-throughput microscopy 'QuantitAgeing' pipeline to visualise and quantify ageing defects. This system enables us to investigate if any genetic interventions can prevent ageing upon progerin expression, thereby identifying pathways that are directly involved in driving cellular ageing.

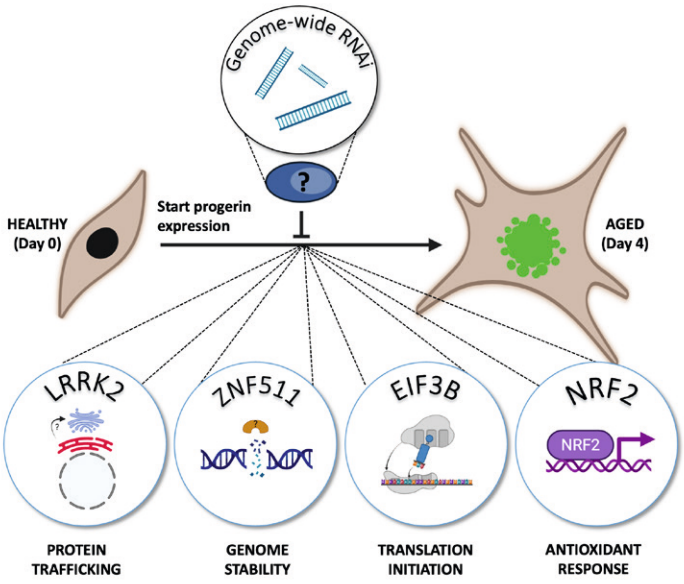
High-throughput screening identifies LRRK2 and ZNF511 as new anti-ageing targets

We previously provided proof-of-principle that we can use our progerin-inducible cell system for high-throughput identification of pathways that drive progerin-induced ageing (Figure 1). Screening a library targeting 320 human ubiquitin ligases for their capacity to prevent cellular ageing, we identified that progerin entrapment of the proteostatic master regulator NRF2 partially drives cellular ageing. We similarly performed a kinome (~2000 targets) and genome-wide RNAi screen. The kinome screen revealed leucine-rich repeat kinase 2 (LRRK2) as a novel regulator of progerin-induced ageing. LRRK2 knockdown prevents progerin from inducing ageing and reverses established ageing defects in primary HGPS patient cells. Interestingly, *LRRK2* mutations are a well-known cause of Parkinson's disease (PD). These data suggest that the accelerated ageing in HGPS and PD may have shared pathological roots.

Anti-ageing candidates identified from the genome-wide RNAi screen include a previously uncharacterised zinc finger protein (ZNF511), which, upon knockdown, not only prevents progerin-induced ageing, but also reverses ageing defects in cells from physiologically aged individuals. We observed that during ageing, there is an increased formation of nuclear foci that contain both ZNF511 and DNA damage repair proteins. These results suggest a potential role for ZNF511 in premature and physiological ageing through the modulation of DNA damage repair.

FUTURE DIRECTIONS

Our future work will continue to mechanistically unravel the molecular pathways that regulate ageing. LRRK2 is a major regulator of the endolysosomal system. We will apply molecular reporter assays to evaluate how the endolysosomal system is affected in HGPS and physiological ageing in the context of LRRK2 activity. We will further use CRISPR editing to endogenously tag LRRK2 in order to perform pulldown studies and determine how the LRRK2 interactome alters with ageing. We will also investigate the role of ZNF511 in regulating genomic stability by determining whether the formation of ZNF511 nuclear foci is specific to certain types of DNA damage and whether ZNF511 levels affect specific types of DNA repair. Additionally, we will determine the protein and DNA interactomes of ZNF511. Lastly, we will expand our molecular toolbox by creating additional inducible cellular ageing models and determine to what extent the anti-ageing drivers we identified are capable of preventing stressors that drive cellular ageing.



▲ **Figure 1**

High-throughput siRNA screenings have revealed that knockdown of LRRK2, ZNF511, EIF3B and NRF2 reduce progerin-induced cellular ageing. Created with Biorender.com.

SELECTED PUBLICATIONS

Adriaens C, Serebryannyy LA, Feric M, Schibler A, Meaburn KJ, Kubben N, Trzaskoma P, Shachar S, Vidak S, Finn EH, Sood V, Pegoraro G and Misteli T (2018) Blank spots on the map: some current questions on nuclear organization and genome architecture. *Histochem Cell Biol*, 150:579–592

Kreienkamp R*, Graziano S*, Coll-Bonfill N*, Bedia-Diaz G, Cybulla E, Vindigni A, Dorsett D, Kubben N, Batista LFZ and Gonzalo S (2018) A cell-intrinsic interferon-like response links replication stress to cellular aging caused by progerin. *Cell Rep*, 22:2006–2015

*indicates joint contribution

Shen Y, Kubben N, Candia J, Morozov AV, Misteli T and Losert W (2018) RefCell: multi-dimensional analysis of image-based high-throughput screens based on "typical cells." *BMC Bioinformatics*, 19:427

Edward **Lemke**

> How do the dynamics of intrinsically disordered proteins affect gene regulation & ageing?

POSITIONS HELD

Since 2018 Adjunct Director, Institute of Molecular Biology (IMB), Mainz

Professor of Synthetic Biophysics, Johannes Gutenberg University Mainz (JGU)

2009 – 2017 Group Leader, European Molecular Biology Laboratory (EMBL), Heidelberg (visiting since 2018)

2005 – 2008 Postdoc, The Scripps Research Institute, La Jolla

EDUCATION

2005 PhD in Chemistry, Max Planck Institute for Biophysical Chemistry & University of Göttingen

2001 Diplom in Chemistry, Technical University of Berlin

2001 MSc in Biochemistry, University of Oklahoma

GROUP MEMBERS

Staff Scientist Christian Schäfer

Postdocs Rajanya Bhattacharjee, Sabrina Giofrè, Cosimo Jann, Anastasia Lopatina, Lawanya Natarajan, Hao Ruan, Tom Scheidt

PhD Students Marius Jung, Sara Mingu, Lukas Schartel, Chenxi Yang

Lab Manager Joana Caria

Technology Manager Nike Heinss

Group Administrator Carmen Mouzaffar

DISCOVER MORE

OVERVIEW

We focus on studying intrinsically disordered proteins (IDPs), which constitute up to 50% of the eukaryotic proteome. IDPs are most famous for their involvement in neurodegenerative diseases of ageing like Alzheimer's, Parkinson's and Huntington's disease. The ability of IDPs to exist in multiple conformations is considered a major driving force behind their enrichment during evolution in eukaryotes, but it also comes with the risk of molecularly 'ageing' into states that ultimately cause disease. Studying biological machineries containing such dynamic proteins is a huge hurdle for conventional technologies. Using a question-driven, multidisciplinary approach paired with novel tool development, we have made major strides in understanding the biological dynamics of such systems from the single molecule to the whole cell level. Fluorescence tools are ideally suited to studying the plasticity of IDPs, as their non-invasive character permits a smooth transition between *in vitro* (biochemical) and *in vivo* (in cell) studies. In particular, single-molecule and super-resolution techniques are powerful tools for studying the spatial and temporal heterogeneities that are intrinsic to complex biological systems. We synergistically combine this effort with cutting-edge developments in chemical and synthetic biology, microfluidics and microscope engineering to increase the throughput, strength and sensitivity of the approach as a whole.

RESEARCH HIGHLIGHTS

Our strong focus on understanding the mechanisms of IDP function and molecular ageing is both driven by and driving novel tool developments for "in-cell/*in situ* structural biology." This comprises a synergistic effort of chemical/synthetic biology and biotechnology with precision fluorescence-based technology/nanoscopy/single-molecule/super-resolution/microfluidics development. A major technical breakthrough of my lab was the ability to engineer "click"able functionalities into any protein *in vitro* and *in vivo*. This genetic code expansion (GCE) approach has the potential to become a true GFP (fusion protein) surrogate strategy, with the

major advantage being that superior synthetic dyes can be coupled with residue-specific precision anywhere in a protein. This opens up new avenues in single-molecule fluorescence and super-resolution microscopy. More recently, we have been able to merge our understanding of protein disorder and synthetic biology to design new membraneless organelles dedicated to protein engineering and RNA editing *in situ*. These custom organelles do not just execute a distinct second genetic code inside the cells; their bottom-up design also enables us to learn how phase separation can be used to generate new functions in eukaryotes. Our findings also have wider implications for understanding gene regulatory and stress-based mechanisms that are carried out by distinct, naturally-occurring organelles and play vital roles in regular cell function, as well as in ageing. These precision tools enable us to make even the most complex molecular machinery visible to our core methodologies, which are based on time-resolved multiparameter and nanoscopy tools. This allows innovative approaches to study the heterogeneity of IDPs *in vitro* and *in vivo*. We discovered a distinct ultrafast protein-protein interaction mechanism that can explain how nuclear pore complexes (NPCs) efficiently fulfil their central role in cellular logistics and how nuclear transport can be both fast and selective at the same time.

Most recently, all the seemingly different efforts of my lab in chemical/synthetic biology and fluorescence biophysics concluded in studies that visualised for the first time the permeability barrier of the functional nuclear pore complex *in situ*, which is responsible for regulating all the traffic between the cytoplasm and the nucleoplasm. The key finding that IDPs in this machinery can become a solvent for themselves and that this is accompanied by a giant conformational change in the protein showcases a genuine example of how knowledge from polymer science can improve our understanding of biological systems.

FUTURE DIRECTIONS

IDPs lack a stable structure and can easily misfold to the amyloid state and aggregate, resulting in their prominent role in many age-related diseases. This intrinsic risk must be outweighed by multiple advantages to explain their enrichment in the evolution of more complex species, but we are only beginning to understand this. IDPs are highly multifunctional and, due to their multivalency and large, disordered regions, they can function as dynamic scaffold platforms. We combine chemical and synthetic biology approaches to enable non-invasive, multi-colour high- and super-resolution studies of activity-dependent protein conformation changes in living cells, enabling fluorescence-driven *in situ* structural biology. The key point is that the enhanced spatial and temporal resolution offered by our fluorescent methods will enable us to detect rare events and unexpected behaviours inside cells, which we will then use to identify and understand IDP multifunctionalities that are clearly distinguishable from their normal mode of action. For example, nucleoporins (Nups) normally function in the nuclear pore complex (NPC), but in fact many IDP-Nups have diverse roles, such as in pathogen-host interactions, and can even shuttle away from the NPC to function in gene regulatory processes. Moreover, fusions of *Nup98* with transcription factors (such as *NHA9*) are known to be linked to leukaemia. Our work is accompanied by rigorous analysis of the physicochemical properties of IDPs and examines to what extent simple, known polymer concepts such as phase separation can be used to describe the function of IDP biopolymers *in vivo*. We have now shown that NHA9 can populate distinct micro- and macrophases. The next step is to study if and how its different functions with respect to gene expression are linked to very different assembly states.

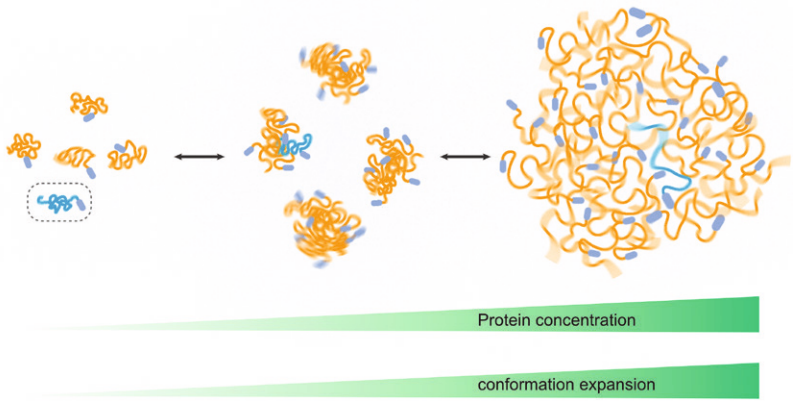


Figure 1 ▶

Scheme illustrating the different assembly states of the oncofusion protein NHA9. The disordered domain is the driving force behind NHA9 self-assembly, and our data revealed that the disordered domain became increasingly expanded from the dilute state to nanoclusters and macroscopic condensates, which might lead to different gene regulatory outcomes.

SELECTED PUBLICATIONS

Schartel L, Jann C, Wierczeiko A, Butto T, Mündnich S, Marchand V, Motorin Y, Helm M, Gerber S and Lemke EA (2024) Selective RNA pseudouridinylation *in situ* by circular gRNAs in designer organelles. *Nat Commun*, 15:9177

Yu M*, Heidari M*, Mikhaleva S*, Tan PS*, Mingu S, Ruan H, Reinkemeier CD, Obarska-Kosinska A, Siggel M, Beck M, Hummer G# and Lemke EA# (2023) Visualizing the disordered nuclear transport machinery *in situ*. *Nature*, 617:162–169

Reinkemeier CD and Lemke EA (2021) Dual film-like organelles enable spatial separation of orthogonal eukaryotic translation. *Cell*, 184:4886–4903.e21

*indicates joint contribution, #indicates joint correspondence

Katja **Luck**

> We structurally resolve protein interactomes to study mechanisms of health & disease.

POSITIONS HELD

Since 2020 Emmy Noether Group Leader, Institute of Molecular Biology (IMB), Mainz

2013 – 2019 Postdoctoral Fellow, Dana-Farber Cancer Institute and Harvard Medical School, Boston

2007 – 2008 Research Assistant, EMBL, Heidelberg

EDUCATION

2012 PhD in Bioinformatics, University of Strasbourg

2007 Diplom in Bioinformatics, Friedrich Schiller University Jena

GROUP MEMBERS

Postdocs Jesus Alvarado Valverde

PhD Students Caroline Barry, Milena Djokic, Joost Früsemers, Johanna Lena Geist, Jann Rusch, Joelle Morgan Strom

Master's Student Evelyn Eiswert

Lab Manager Mareen Welzel

Research Assistant Eleni Aretaki

DISCOVER MORE

OVERVIEW

Cells function because their molecular components (DNA, RNA, proteins) interact with each other. This complex network of molecular interactions mediates all cellular functions and organisation. Genetic and environmental insults perturb these interactions, causing disease. Because of technical limitations, we lack a comprehensive structural and functional understanding of all the protein interactions in human cells, hindering our ability to understand physiological and pathological molecular mechanisms. To tackle this, my lab develops novel computational and experimental methods to identify protein interaction interfaces and, based on this, obtains information on their molecular functions. We use protein interaction interface information to predict the pathogenicity of genetic variants and develop integrative omics data approaches to generate testable mechanistic hypotheses. We apply our approaches to study proteins associated with neurodevelopmental disorders (NDDs) and proteins functioning in protein quality control and mRNA splicing, as well as chromatin remodelling, together with our collaborators.

RESEARCH HIGHLIGHTS

Proteins exhibit a modular architecture consisting of folded domains and disordered regions, which can carry short linear motifs. Proteins use these different modules to mediate binding to partner proteins. We found that AI-based structure prediction tools such as AlphaFold perform differently when predicting protein complex structures depending on the type of interface, i.e. domain-domain or domain-motif, and the length of the protein chains submitted for structural modelling, with longer chains performing more poorly (Geist *et al.*, 2024, *Bioinformatics*, Lee *et al.*, 2024, *Mol Syst Biol*). We published a review this year describing the biases in AI-based structure prediction tools, how they likely arise from biases in the training data, and how this can be avoided (Strom and Luck, 2025, *Curr Opin Struct Biol*). To improve our ability to predict domain-motif interfaces for protein-protein interactions (PPIs),

we developed a random forest model that uses existing information on types of domain-motif interfaces and sequence pattern searches to guide AlphaFold towards the most likely interacting protein regions, and then only submits those for structural modelling. We applied this strategy to 52,000 human PPIs and obtained good structural models of domain-motif interfaces for more than 1,300 PPIs. We tested whether these predicted interfaces could help us decide if mutations in patients were likely to disrupt protein function or not, based on whether they occurred at an interface position. Most mutations identified in patients remain uncharacterised, especially those in disordered protein regions. As a result, most patients remain without a genetic diagnosis and we do not advance in our understanding of disease mechanisms. We used our structural models to predict that 1,200 variants in motifs are likely to be deleterious to protein binding. These predictions were supported by experimental validation of six predicted interfaces and testing the effects of 23 mutations on PPIs. Importantly, our structure-based approach more accurately predicts the effects of mutations in motifs than the state-of-the-art variant effect predictor AlphaMissense. This work is in revision at *Nat Struct Mol Biol* and available on *bioRxiv* (Hubrich *et al.*, 2025). We also successfully lent our expertise in structural modelling and PPI measurements to other groups (Gabele *et al.*, *Cell Reports,* 2025, Mehra *et al.*, *Nature Cell Biol*, accepted, Börgel *et al.*, *Nat Struct Mol Biol*, in revision).

FUTURE DIRECTIONS

We will continue developing tools to predict and experimentally characterise protein interaction interfaces, with the goal of studying interactions involving disordered regions. Such interactions are often involved in the formation of liquid-like condensates, which we aim to study in the context of mRNA splicing and protein homeostasis; the latter is funded as part of the CRC 1551 in collaboration with the Beli lab (IMB), as well as the Kukharenko and Kremer labs (Max Planck Institute for Polymer Research). We are furthermore working towards a systematic resource of clustered protein interaction interfaces to explore the diversity and evolutionary aspects of protein binding modes.

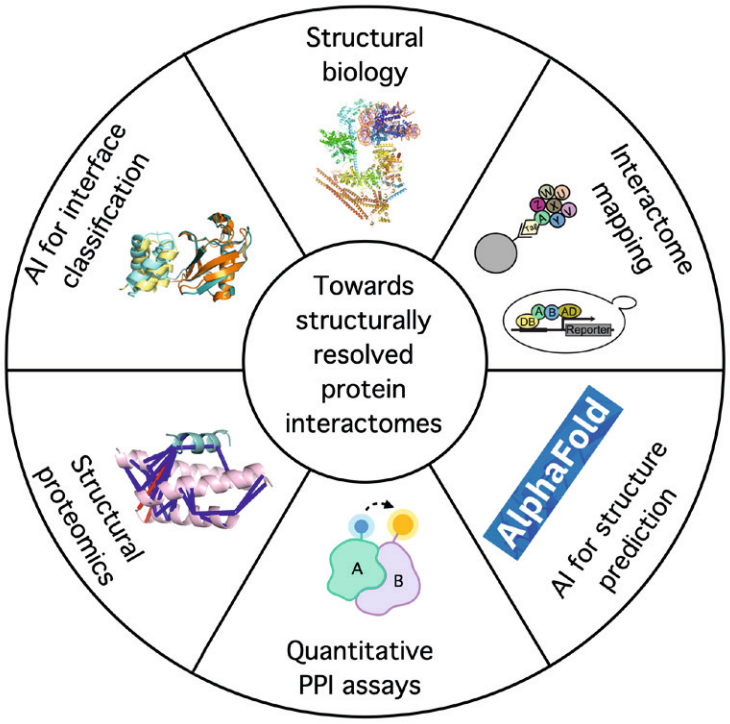


Figure 1

Towards structurally resolved protein interactomes via integrative systems biology.

SELECTED PUBLICATIONS

Geist J*, Lee CY*, Strom JM, Naveja JJ# and Luck K# (2024) Generation of a high confidence set of domain-domain interface types to guide protein complex structure predictions by AlphaFold. *Bioinformatics*, 40:btae482

Lee CY*, Hubrich D*, Varga JK*, Schäfer C, Welzel M, Schumbera E, Djokic M, Strom JM, Schönfeld J, Geist JL, Polat F, Gibson TJ, Keller Valsecchi CI, Kumar M, Schueler-Furman O# and Luck K# (2024) Systematic discovery of protein interaction interfaces using AlphaFold and experimental validation. *Mol Syst Biol*, 20:75-97

Ebersberger S*, Hipp C*, Mulorz MM*, Buchbender A, Hubrich D, Kang HS, Martínez-Lumbreras S, Kristofori P, Sutandy FXR, Llacsahuanga Allcca L, Schönfeld J, Bakisoglu C, Busch A, Hänel H, Tretow K, Welzel M, Di Liddo A, Möckel MM, Zarnack K, Ebersberger I, Legewie S, Luck K#, Sattler M# and König J# (2023) FUBP1 is a general splicing factor facilitating 3′ splice site recognition and splicing of long introns. *Mol Cell*, 83:2653-2672.e15

*indicates joint contribution, #indicates joint correspondence

Brian **Luke**

> Reducing mutation rates may prevent some age-associated diseases.

POSITIONS HELD

Since 2017	Adjunct Director, Institute of Molecular Biology (IMB), Mainz
	Heisenberg Professor, Johannes Gutenberg University Mainz (JGU)
2014 – 2017	Group Leader, Institute of Molecular Biology (IMB), Mainz
2009 – 2014	Group Leader, Centre for Molecular Biology (ZMBH), University of Heidelberg
2005 – 2009	Postdoc, Swiss Federal Institute of Technology Lausanne (EPFL)
2005	Postdoc, Swiss Federal Institute of Technology Zurich (ETH)

EDUCATION

2005	PhD in Biochemistry, Swiss Federal Institute of Technology Zurich (ETH)
1999	BSc in Biology, Queen's University, Ontario

GROUP MEMBERS

Postdocs Fabio Bento, Sacha Heerschop, Natalie Schindler

PhD Students Rodolfos Danalatos, Eduardo Gameiro*, Kristi Jensen, Sana'a Khraisat*, Nina Lohner, Matteo Longaretti, Zukhra Stamgaliyeva, Varvara Verkhova*, Carolin Wagner, Maya Wilkens*

Master's Students Tobias Frank, Luca Kindinger, Sophia Sergi

Bachelor's Students Florian Hippe, Pauline Raifschnaider

Student Assistant Linus Nuppnau

Technicians Dennis Knorr, Stefanie Reimann

Personal Assistant Christiane Stürzbecher

*indicates joint PhD student

DISCOVER MORE

OVERVIEW

Ageing is associated with impaired organ, tissue and cellular function, as well as the increased occurrence of diseases such as cancer, Alzheimer's and osteoporosis, to name a few. The loss of organ function, or disease progression, eventually leads to death. In response, we are frequently prescribed myriad medications to treat age-related symptoms, including hypertension, arthritis, inflammation, etc. Although the above description of ageing appears rather pessimistic and even complicated, recent research has indicated that the ageing process may be easier to deal with than previously thought.

Although the tissues, organs and cells that are affected by ageing may differ, the affected molecular machineries within the cells are identical. We have learned that neurodegeneration and cancer development, both age-related diseases, are likely due to defective maintenance of chromosomal DNA. We have now identified that four cellular processes are consistently dysfunctional in ageing cells: genome maintenance, epigenetic regulation, the preservation of telomeres, and the upkeep of protein function. Hence, rather than treating diseases in an organ/tissue-specific manner, which can quickly accumulate, we should be treating the molecular dysfunctions, as there are only four of them. Such an approach will help to both alleviate and prevent age-related symptoms.

RESEARCH HIGHLIGHTS

We are using a model system, *S. cerevisiae*, to assess how genomic mutations accumulate during ageing and investigate how this may be regulated or ameliorated. It is well established that rates of DNA mutation increase with age. Furthermore, organisms with low mutation rates tend to live longer than organisms with high mutation rates. It is not clear whether mutational frequency is a cause or consequence of ageing. The most frequent DNA mutation that occurs on a daily basis is the erroneous misincorporation of ribonucleotides instead of deoxyribonucleotides into the genome during DNA replication. The inserted ribonucleotide monophosphates (rNMPs) are normally removed by ribonucleotide excision

repair (RER) proteins, which are orchestrated by the ribonuclease RNase H2. When RNase H2 is mutated or deleted, rNMPs accumulate and lead to 2-5 base pair deletions throughout the genome. The deletions are due to the activity of topoisomerase I (Top1) (Figure 1).

Using a specific reporter, we were able to show that old cells have more Top1 mutations than young cells. Although increased Top1 levels can lead to more mutations, we did not see that Top1 levels were increased in old compared to young cells. We used a well-characterised DNA polymerase mutant that incorporates fewer rNMPs into the genome than a wild-type copy. We found that cells with less rNMPs have an increased lifespan. This suggests that rNMPs in the genome may contribute to ageing.

Multiple interventions that extend lifespan and healthspan have been discovered. Caloric restriction (CR) has consistently been demonstrated to improve longevity and healthspan in eukaryotic organisms ranging from yeast to humans. We demonstrated that CR is also able to reduce Top1-related mutations, even in young cells. This suggests that, in part, CR may extend lifespan by decreasing the mutagenic load of aged cells.

By understanding how rNMP insertion and excision are controlled, we may be able to better understand and control mutation rates during the ageing process. Leveraging these processes may eventually result in the prevention of age-related disease and hence healthy ageing.

FUTURE DIRECTIONS

Although we have identified an increase in the Top1 mutation signature at rNMPs, we do not have a good understanding of the mechanistic details involved. It is possible that RNase H2 is less efficient or less expressed in old cells. We are currently generating RNase H2 antibodies to test these ideas. It is also possible that NTP to dNTP ratios are altered in old compared to young cells; this is another hypothesis that is being actively pursued. We are collaborating with the Padeken lab (IMB) to determine if these relationships are conserved in *C. elegans*. Preliminary data has indicated that the loss of RNase H2 activity shortens the lifespan of adult worms. Finally, we will employ genetic and chemical genetics to probe pathways that extend and shorten lifespan and assess their effects on Top1 mutagenesis at rNMPs.

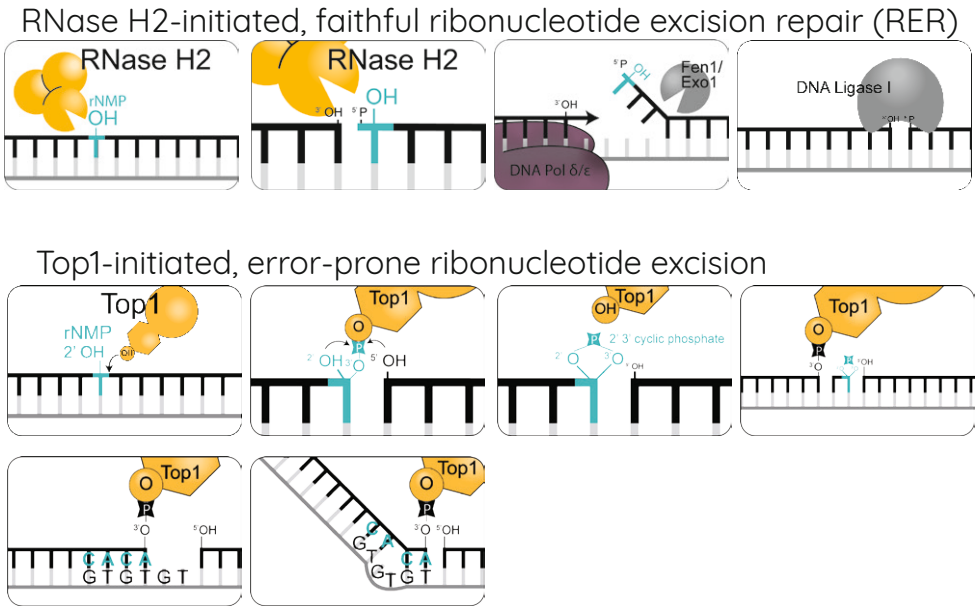


Figure 1

rNMPs are removed in an error-free manner by the activity of the RNase H2 enzyme. When RNase H2 is absent, Top1 removes the rNMPs, which can result in the generation of deletion mutations.

SELECTED PUBLICATIONS

Schindler N*, Tonn M*, Kellner V, Fung JJ, Lockhart A, Vydzhak O, Juretschke T, Möckel S, Beli P, Khmelinskii A and Luke B (2023) Genetic requirements for repair of lesions caused by single genomic ribonucleotides in S phase. *Nat Commun*, 14:1227

Misino S, Busch A, Wagner C, Bento F and Luke B (2022) TERRA increases at short telomeres in yeast survivors and regulates survivor associated senescence (SAS). *Nucleic Acids Res*, 50:12829-12843

Wagner CB and Luke B (2022) DNA-RNA hybrids at telomeres in budding yeast. *Methods Mol Biol*, 2528:145-157

*indicates joint contribution

Christof **Niehrs**

> We explore regulatory nucleic acid modifications in early embryonic development.

POSITIONS HELD

Since 2021	Director, Centre for Healthy Ageing (CHA), Mainz
Since 2010	Founding & Scientific Director, Institute of Molecular Biology (IMB), Mainz
	Professor, Johannes Gutenberg University Mainz (JGU)
Since 2000	Professor of Molecular Embryology, German Cancer Research Center (DKFZ), Heidelberg
Since 1994	Head of Division "Molecular Embryology", German Cancer Research Center (DKFZ), Heidelberg
1990 – 1993	Postdoc, University of California Los Angeles (UCLA)

EDUCATION

1997	Habilitation in Biology, University of Heidelberg
1990	PhD in Biology, European Molecular Biology Laboratory (EMBL) & University of Heidelberg
1985	Diplom in Biochemistry, Free University of Berlin

GROUP MEMBERS

Senior Research Associates Michael Musheev, Lars Schomacher

Postdocs Amitava Basu, Alexandr Gopanenko, Ivan Laptev, Marcel Misak, Trang Trhu Nguyen, Rintu Umesh, Ettore Zapparoli

PhD Students Jasmin Dehnen, Deepa Jayaprakashappa, Johanna Melanie Schott, Shubhanjali Shubhanjali, Umut Taşdelen

Lab Manager Sandra Rölle

Technicians Laura Frosch, Carola Scholz

Personal Assistant Jutta Karn

DISCOVER MORE

OVERVIEW

Although DNA is commonly perceived as a static molecule, genomic nucleobases are in fact physiologically modified by a variety of chemical modifications. These DNA modifications are deposited in the genome in a site-specific manner and are known or suspected to epigenetically regulate gene expression. Typically, DNA modifications are recognised by specific reader proteins and can be reversed by a variety of enzymatic mechanisms. We study which DNA modifications occur in the mammalian genome, how and where they are deposited, what biological role they play, and how they are recognised and removed. We use ultrasensitive mass spectrometry to identify and quantify DNA modifications in mammalian cells. We employ next-generation sequencing and computational analysis to identify modification sites genome-wide. Recently, we have also been studying RNA modifications. We characterise the roles of proteins involved in depositing, reading and removing modifications in embryonic stem cells, *Xenopus* embryos and mice.

RESEARCH HIGHLIGHTS

The role of 5-formylcytosine in DNA and RNA

The study of oxidised 5-methylcytosine (5mC) derivatives has long been central to understanding DNA methylation and gene regulation. Among these derivatives, we have focused on 5-formylcytosine (5fC) and asked whether it acts solely as an intermediate in active DNA demethylation or functions independently as an instructive, regulatory mark. We studied 5fC's potential role as an epigenetic regulator in *Xenopus* embryos during zygotic genome activation (ZGA), a key developmental phase marked by the transition from maternal to embryonic control over gene expression. During early embryonic development, ZGA is a critical period when the zygotic genome becomes transcriptionally active, replacing maternal RNA with its own genetic programme. We discovered that 5fC forms distinct chromocenters in the nuclei of *Xenopus* embryos during ZGA, which are associated with the perinucleolar compartment (PNC). These 5fC chromocenters are transient and

colocalise with RNA polymerase III (Pol III) components in the PNC. Genomic profiling further corroborated that 5fC is enriched at Pol III target loci, notably at tRNA genes where 5fC correlates with active chromatin marks, indicating a role in stimulating transcription. Further experiments demonstrated that 5fC functions as an instructive, activating DNA mark distinct from 5mC, promoting Pol III–dependent transcription during the ZGA transition. Thus, 5fC is the second epigenetic DNA mark besides 5mC in vertebrates (Parasyraki *et al.*, 2024, *Cell*).

Following the establishment of 5fC as an epigenetic mark in DNA, we wondered about the potential role of its RNA homolog, f5C. In mammals, f5C occurs at position 34 of mitochondrial tRNA methionine (*mt-tRNAMet*), where it expands codon recognition from AUG to both AUG and AUA, sustaining efficient mitochondrial translation. It is formed by oxidation of m5C, which is then oxidised via hm5C to f5C by the dioxygenase ALKBH1. Putative f5C has also been reported in mRNA (mouse liver, HEK293T, yeast), but the levels are extremely low, suggesting sub-stoichiometric oxidation of m5C rather than specific site installation. TET enzymes were proposed as RNA cytidine formylases, consistent with their ability to generate 5fC in DNA via an analogous oxidative pathway.

We analysed f5C in the RNA of mESCs using LC-MS/MS and chemical-assisted sequencing. We found that the previously reported pyridine-borane sequencing misidentifies N4-acetylcytidine (ac4C) and unmodified, hyper-reactive cytidines in a CUMC context as f5C. To overcome these limitations, we developed FIBo-seq, a method with enhanced specificity and sensitivity for f5C sequencing. Using FIBo-seq, we found no f5C sites in mRNA. Instead, the bulk of mammalian f5C resides in the well-established mitochondrial tRNA methionine (*mt-tRNA-Met*) and is mediated by ALKBH1. These results argue against an instructive function for f5C outside of tRNA in mammals (Dehnen *et al.*, 2025, *Nat Commun*).

FUTURE DIRECTIONS

A key open question is whether 5fC in DNA functions as an active regulatory mark in mammals, as it does in *Xenopus*. In mouse ESCs, 5fC is enriched at active enhancers and dynamic chromatin, consistent with a role in gene activation. Beyond classical tRNA/5S loci, Pol III also occupies "extra-TFIIIC" (ETC) sites linked to CTCF and SINEs that may organise long-range chromatin. We hypothesise that 5fC facilitates or stabilises Pol III binding at ETCs; upcoming work will test 5fC-ETC colocalisation and functional impact. With regard to f5C in RNA, it will be interesting to use FIBo-seq to analyse non-mammalian systems and test if the modification is present outside *mt-tRNAMet*. Mapping where f5C occurs across organisms pinpoints when the modification emerged or died out. Other organisms may place f5C in rRNAs or even mRNAs, with effects on translational fidelity or proteome tuning. If pathogens rely on f5C for efficient translation, the enzymes may be useful as drug targets.

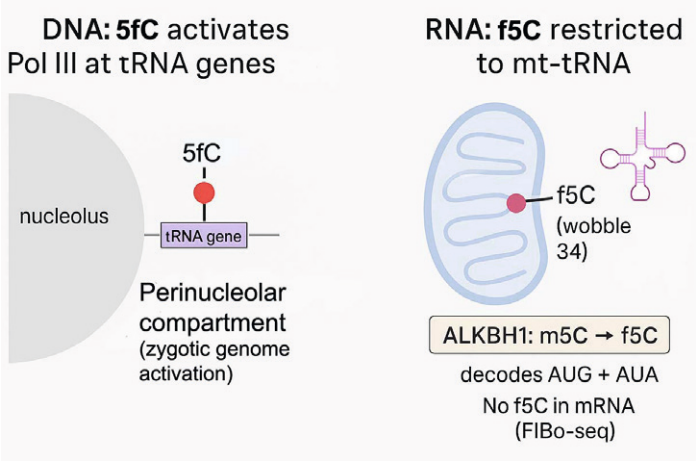


Figure 1

The different roles of 5-formylcytosine in DNA and RNA. Left: Model for how 5fC acts as an epigenetic DNA mark to stimulate transcription of *tRNA* tandem repeat genes by Pol III. 5fC accumulates in the perinuclear compartment (PNC), where Pol III target gene transcription is concentrated. Right: Model for how f5C acts as a specific epitranscriptomic RNA mark in mitochondrial tRNA methionine (*mt-tRNAMet*), where it is essential for codon expansion during translation

SELECTED PUBLICATIONS

Parasyraki E*, Mallick M*, Hatch V*, Vastolo V, Musheev MU, Karaulanov E, Gopanenko A, Moxon S, Méndez-Lago M, Han D, Schomacher L, Mukherjee D and Niehrs C (2024) 5-Formylcytosine is an activating epigenetic mark for RNA Pol III during zygotic reprogramming. *Cell*, 187:6088–6103.e18

Zoller JA*, Parasyraki E*, Lu AT, Haghani A, Niehrs C# and Horvath S# (2023) DNA methylation clocks for clawed frogs reveal evolutionary conservation of epigenetic aging. *GeroScience*, 46:945–960

Musheev MU*, Schomacher L*#, Basu A*, Han D, Krebs L, Scholz C and Niehrs C# (2022) Mammalian N1-adenosine PARylation is a reversible DNA modification. *Nat Commun*, 13:6138

*indicates joint contribution, #indicates joint correspondence

Jan **Padeken**

> We focus on the relationship between stress & epigenetic changes as organisms age.

POSITIONS HELD

Since 2022 Group Leader, Institute of Molecular Biology (IMB), Mainz

2013 – 2022 Postdoc, Friedrich Miescher Institute, Basel

EDUCATION

2013 PhD in Cell Biology, Max Planck Institute of Immunobiology and Epigenetics, Freiburg

2009 Diplom in Biology, Albert Ludwig University of Freiburg

GROUP MEMBERS

Postdoc Styliani-Eirini Kanta

PhD Students Ishita Amar, Valerie Arz, Lisa Fol*, Konstantinos Kydonakis, Anton Musabirov, Rosa Herrera Rodriguez

Master's Students Luisa Dietz, Vanessa Mayer, Franziska Roithner

Student Assistants Anne Armbruster, Kimiya Faraji, Tim Müller

*indicates joint PhD student

DISCOVER MORE

OVERVIEW

The epigenetic packaging of our genome is essential for maintaining cellular function and identity over time. Stress and ageing, however, can alter or erode the spatial separation of transcriptionally permissive euchromatin and repressive heterochromatin. Lysine 9 methylation on histone H3 (H3K9me) is a defining modification of heterochromatin. In multicellular eukaryotes, heterochromatin has two main functions. First, it silences repetitive sequences to ensure genome stability and prevent toxic R-loops; second, it maintains the silencing of genes during and post-development to ensure a stable differentiated state. Thus, it is not surprising that the loss of appropriately targeted heterochromatin is associated with ageing and that mutants deficient in heterochromatin display signs of premature ageing. In our lab, we explore the mechanisms behind this phenomenon from two sides. We ask how external stress can alter epigenetic silencing, resulting in the transient or long-term establishment of heterochromatin, and we ask how loss of heterochromatin enhances or triggers the loss of proteostasis and transcriptional variability.

RESEARCH HIGHLIGHTS

How does persistent DNA damage alter heterochromatin after acute exposure, and are these changes maintained in old cells?

Rare genetic diseases have been central in linking DNA damage to ageing. Cockayne syndrome (CS) is caused by autosomal recessive mutations in either the *CSA* or *CSB* gene and results in persistent DNA damage. *CSA* and *CSB* are essential for initiating transcription-coupled nucleotide excision repair (TC-NER), a DNA damage response pathway that repairs DNA lesions (e.g. UV-induced pyrimidine dimers) blocking RNA polymerase II at sites of active transcription. CS patients therefore accumulate persistent DNA damage in transcribed genes. This manifests in a complex, multi-organ set of clinical features, including premature ageing, neurodegeneration, dysfunctional mitochondria, retarded development

and loss of subcutaneous fat and muscle function. This progressive, multi-tissue pathology requires a simple but well-characterised model organism such as *C. elegans*, which, in contrast to the mouse, mimics the clinical features of CS patients. Survival of persistent UV damage is tightly linked to genome-wide chromatin changes. Interestingly, the phenotypes observed in CS patients (or the worm model) are mimicked by the loss of H3K9me. Indeed, H3K9me and the histone methyltransferase (HMT) MET-2 are essential in the CS model.

Using our expertise in chromatin biology, we describe the acute and persistent changes in heterochromatin upon persistent UV damage to ultimately answer how H3K9me protects an organism from the persistent DNA damage and premature ageing characteristic of CS.

What are the mechanisms that mediate *de novo* establishment of heterochromatin?

The importance of H3K9me in the stress response, as well as its role in silencing tissue-specific genes and potentially active transposable elements, implies that H3K9me can be highly dynamic. To understand the *de novo* establishment and maintenance of heterochromatin domains on a mechanistic level, we developed a unique system to identify sequences that are sufficient to trigger *de novo* recruitment of the two H3K9-specific HMTs and identify the proteins that are essential for establishing the H3K9me domain. We will use this to screen for factors that are essential for the establishment vs. maintenance of heterochromatin and link these pathways to the stress response and premature ageing.

What regulates chromatin compaction and transcriptional noise at heterochromatic genes in parallel to H3K9me?

The transcription levels of genes between cells of the same cell type is remarkably invariable in young, healthy organisms. During ageing, however, cell-to-cell variability of gene transcription increases across organisms. We previously showed that loss of H3K9me results in cell-type-specific gene derepression (Methot *et al.*, 2021, *Nat Cell Biol*). We also observed that this specific form of derepression was characterised by high cell-to-cell transcriptional variability, even between cells of the same tissue. Because this increase in gene expression stochasticity mirrors the increased variability observed in old or senescent cells, we have established an automated imaging-based method to quantitatively screen for mediators of both chromatin compaction and transcriptional noise.

FUTURE DIRECTIONS

Ultimately, the projects above will give us a better understanding of how heterochromatin and its loss during ageing impact the processes that are thought to drive ageing, like the DNA damage response and loss of protein homeostasis. It will also give us a basis to further explore how, in general, epigenetic memory is shaped during an organism's life and how it impacts normal ageing or progeria models such as CS and Hutchinson-Gilford progeria.

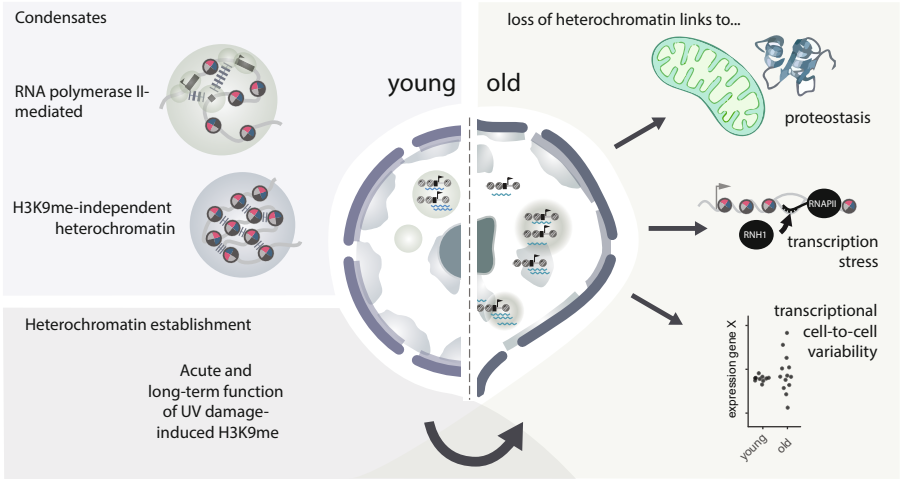


Figure 1

In the lab, we have three interconnected areas of interest: 1) Understanding transcriptional and heterochromatic condensates and their response to temperature stress. 2) How UV damage-induced stress establishes a long term epigenetic memory. 3) Exploring the link between age-induced loss of heterochromatin and the loss of proteostasis and increase in transcriptional noise and stress.

SELECTED PUBLICATIONS

Al-Refaie N, Padovani F, Hornung J, Pudelko L, Binando F, Del Carmen Fabregat A, Zhao Q, Towbin BD, Cenik ES, Stroustrup N, Padeken J, Schmoller KM and Cabianca DS (2024) Fasting shapes chromatin architecture through an mTOR/RNA Pol I axis. *Nat Cell Biol*, 26:1903-1917

Delaney CE, Methot SP, Kalck V, Seebacher J, Hess D, Gasser SM and Padeken J (2022) SETDB1-like MET-2 promotes transcriptional silencing and development independently of its H3K9me-associated catalytic activity. *Nat Struct Mol Biol*, 29:85-96

Methot SP*, Padeken J*, Brancati G, Zeller P, Delaney CE, Gaidatzis D, Kohler H, van Oudenaarden A, Großhans H and Gasser SM (2021) H3K9me selectively blocks transcription factor activity and ensures differentiated tissue integrity. *Nat Cell Biol*, 23:1163-1175

*indicates joint contribution

Stamatis **Papathanasiou**

> We uncover novel tumorigenic mechanisms driven by mitotic errors.

POSITIONS HELD

Since 2023 Group Leader, Institute of Molecular Biology (IMB), Mainz

2015 – 2023 Postdoc, Harvard Medical School and Dana Farber Cancer Institute, Boston

EDUCATION

2015 PhD in Molecular Medicine, National and Kapodistrian University of Athens

2008 MSc in Molecular Medicine, National and Kapodistrian University of Athens

2005 BSc in Molecular Biology and Biotechnology, University of Crete

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Master's Student Mehriban Tasbilek

Lab Manager Evlampia Parcharidou

Research Assistants Leon Enrique Faedrich, Konstantinos Kydonakis

DISCOVER MORE

OVERVIEW

Proper division of the genomic material is fundamental for cell homeostasis. Although cells have mechanisms to ensure error-free division, mistakes are common and a hallmark of disease. One consequence of mitotic errors is the generation of abnormal nuclear structures such as micronuclei and chromosome bridges – common features of nuclear atypia with a central role in the development of cancer. Micronuclei ("MN", Figure 1A) are miniature, extra nuclei that form when a chromosome lags during mitosis and recruits its own nuclear envelope. Micronuclear envelope rupture exposes DNA to the cytoplasm, leading to massive DNA damage. The lesions in the micronucleated chromosome can lead to complex chromosomal rearrangements ("chromothripsis") and ongoing genome instability. Intriguingly, cells with chromothriptic signatures are extremely penetrant in cancer, showing that they can confer a gain of fitness and even drive tumorigenesis. Although the self-amplifying genetic instability and clinical importance of these nuclear abnormalities are well-recognised, we are still missing a detailed understanding of the immediate and long-term non-genetic functional consequences of these mitotic errors.

RESEARCH HIGHLIGHTS

Transgenerational inheritance of chromatin defects from mis-segregated chromosomes

We recently proposed a new model of transgenerational epigenetic instability caused by chromosome mis-segregation in mitosis. Specifically, we discovered a phenomenon of heritable chromatin and transcriptional defects mediated by micronuclei (Papathanasiou *et al.*, 2023, *Nature*). The transcriptional and chromatin states of micronucleated chromosomes are extensively altered; these can be inherited by daughter cells, even after the chromosomes are reincorporated into the normal nuclear environment. Finally, we discovered that persistent transcriptional repression is strongly associated with long-lived DNA damage to these abnormal chromosomes. Taking advantage of this finding, we generated

cellular systems to detect and track damaged chromosomes from micronuclei, e.g. fluorescently labelled MDC1-expressing cells (Figure 1A). We called these structures of reincorporated MN chromosomes with altered chromatin "MN-bodies". The exact circumstances under which cell division errors lead to massive DNA lesions and other chromatin alterations, how they are inherited in progeny cells, and their functional significance all remain a mystery, partly due to a lack of appropriate tools. We develop novel technologies and advanced cellular systems, allowing us to approach these questions from a unique angle. One technology bottleneck was the inability to target specific chromosomes for mis-segregation. We overcame this by developing a novel method to generate "targeted" mis-segregations and micronuclei with *a priori* knowledge of the micronucleated chromosome (Leibowitz*, Papathanasiou* *et al.*, 2021, *Nat Genetics*). This work revealed that micronucleation is a novel side effect of genome editing, with fundamental implications in future clinical applications. We are now further developing these "targeted" approaches and combining them with our cellular systems for tracking mis-segregated chromosomes.

Unravelling the functional properties of abnormal genomes at the single-cell level is fundamental for understanding cellular heterogeneity in disease and for the development of new therapeutic strategies. We are developing new methods that allow us to directly link observed phenotypes to function by combining imaging and "omics" at the single-cell level. We have built an advanced experimental and computational framework by combining long-term live-cell imaging and same-cell, direct single-cell genomics (Simultaneous IMAging and Direct Isolation for sequencing, "SIMADI-seq"). More recently, we further implemented a machine-learning based algorithm for automated lineage tracking within a novel computational framework supporting "on-the-fly" image analysis from live-cell imaging in combination with SimaDi technology ("Ai-SimaDi", Figure 1B). This novel technology will not only allow us to address our questions, but opens a plethora of applications linking phenotypes with lineage information and genomics.

Our discovery that micronuclei are a source of transcriptional heterogeneity and epigenetic instability established a new paradigm for how mitotic errors may be inherently coupled to poorly understood non-genetic cell-to-cell epigenetic variability in disease (e.g. cancer). Our research follows this new perspective on the functional consequences of mitotic errors and abnormal nuclei, which may impact tumour evolution.

FUTURE DIRECTIONS

We will further develop and combine cutting-edge methodologies with advanced systems to track mis-segregated chromosomes over multiple generations. We aim to identify sources of inherited abnormal nuclear structures and characterise their DNA damage/repair dynamics and epigenetic alterations. We will also focus on understanding how transcription dynamics are perturbed in daughter cells upon abnormal mitosis and define chromatin architecture and the higher-order genome organisation of mis-segregated chromosomes. Finally, we will investigate long-term cellular adaptations and assess the tumorigenic potential of abnormal chromosomes. Together, these studies will offer the first comprehensive assessment of non-genetic mechanisms by which errors in mitosis may drive cellular adaptation and tumorigenesis.

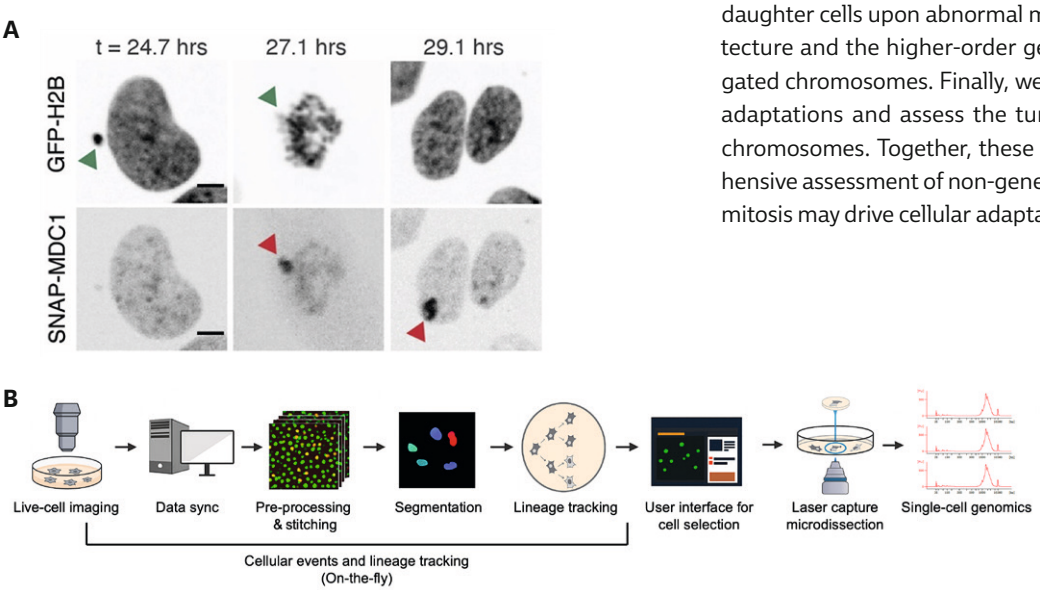

Figure 1

A) Formation of an MN-body (red arrowheads), a type of Mit-body, by reincorporation of a damaged (MDC1) micronucleus (green) into the primary nucleus of a daughter RPE-1 cell ("t" indicates time after release in mitosis, scale bar = 5μm). B) Schematic overview of "Ai-SimaDi", a new machine learning-based framework implementing cell tracking and "SimaDi" for capturing cell lineages for single-cell genomics.

SELECTED PUBLICATIONS

Papathanasiou S#, Mynhier NA, Liu S, Brunette G, Stokasimov E, Jacob E, Li L, Comenho C, van Steensel B, Buenrostro JD, Zhang CZ# and Pellman D# (2023) Heritable transcriptional defects from aberrations of nuclear architecture. *Nature*, 619:184–192

Leibowitz ML*, Papathanasiou S*, Doerfler PA, Blaine LJ, Sun L, Yao Y, Zhang CZ, Weiss MJ and Pellman D (2021) Chromothripsis as an on-target consequence of CRISPR-Cas9 genome editing. *Nat Genet*, 53:895–905

Papathanasiou S, Markoulaki S*, Blaine LJ*, Leibowitz ML, Zhang CZ, Jaenisch R and Pellman D (2021) Whole chromosome loss and genomic instability in mouse embryos after CRISPR-Cas9 genome editing. *Nat Commun*, 12:5855

*indicates joint contribution, #indicates joint correspondence

Katharina **Papsdorf**

> We study how specific lipids extend lifespan.

POSITIONS HELD

Since 2024 Group Leader, Institute of Molecular Biology (IMB), Mainz

2016 – 2023 Postdoctoral Fellow, Stanford University

EDUCATION

2016 PhD in Biochemistry, Technical University of Munich

2011 MSc in Biochemistry, Technical University of Munich

2008 BSc in Biochemistry, Technical University of Munich

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Master's Student Luisa Dietz

Bachelor's Students Anne Armbruster, Jonas Hahn, Marie Sixel

Technician Keshav Gajendra Babu

Student Assistants Nina Becher, Annika Fox

DISCOVER MORE

OVERVIEW

The overarching goal of our lab is to decipher how specific lipids drive cellular changes that induce longevity. Lipids are attractive candidates to study in the context of lifespan regulation as they are ubiquitous components of the human diet. Age progression can be slowed by increasing the abundance of specific lipids in both invertebrates and mice. One well-known example is monounsaturated fatty acids (MUFAs). MUFAs are the main component of olive oil in the Mediterranean diet, correlate with human longevity, and extend lifespan in several species. However, it remains largely unknown how specific lipids, such as MUFAs, protect cells during ageing and if this can be leveraged to promote longevity.

To study the connection between MUFAs and lifespan regulation, we use the nematode worm *C. elegans*. The worm is uniquely positioned because many of its pathways and organelles involved in lipid processing are conserved with mammals, and its short lifespan allows us to perform ageing studies in a laboratory setting. We use a combination of cell biology methods, mass spectrometry, genetics and screening to dissect the functions of specific lipids and the organelles that process them in the context of ageing and longevity.

RESEARCH HIGHLIGHTS

Lipid storage organelles and lifespan

The major lipid reservoirs in cells are lipid droplets. These conserved cellular organelles are central to lipid metabolism because they are specialised for storing lipids and supplying them when cellular energy demand rises. But their role extends beyond being classical storage organelles, as they also sequester lipids that otherwise become detrimental to the cell. Lipid droplets were thought to be inert storage depots, but it is now clear that they are dynamic organelles whose biology is controlled by specialised cellular machinery. Lipid droplets themselves, as well as the lipids they contain, are differentially regulated during ageing and are important for longevity. During my postdoctoral training, I discovered that an increase in lipid droplets is critical for longevity mediated

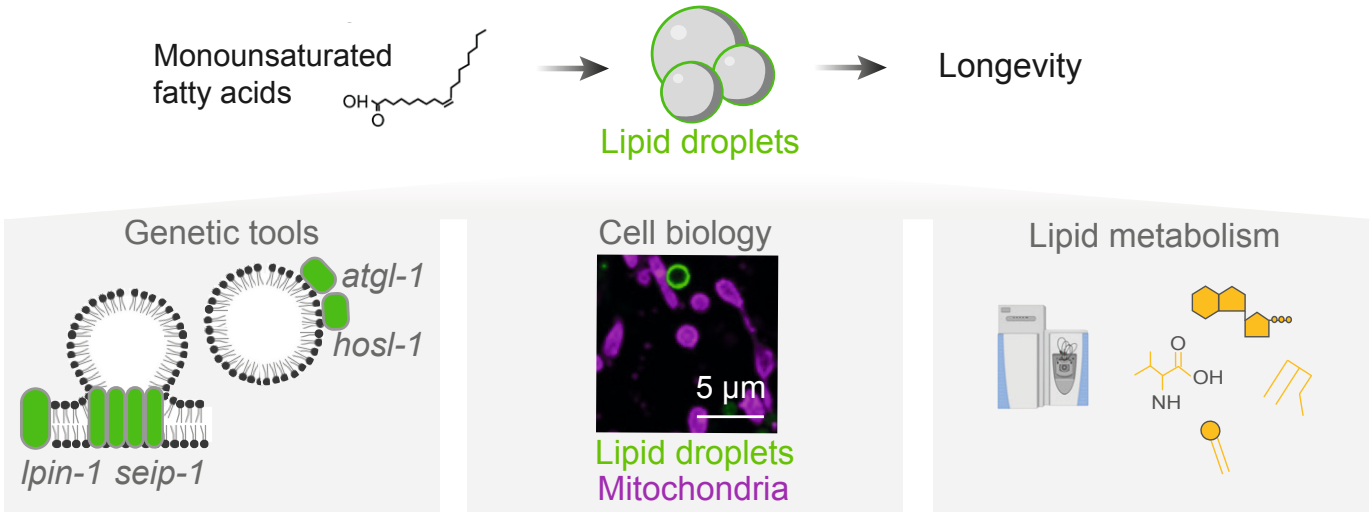
by MUFAs. Importantly, these lipid droplets accumulate only in a designated lipid storage tissue (the *C. elegans* intestine) and not in other tissues. We now study the mechanism by which lipid droplets protect tissues and cellular homeostasis to drive longevity. To this end, we combine tissue-specific and dietary manipulations, mass spectrometry and confocal microscopy coupled with genetic interventions to understand how lipids and their storage influence lifespan.

Organelle contact of lipid droplets during ageing and longevity

Lipid droplets are in frequent contact with other organelles. These interactions are central to lipid homeostasis because lipid droplet biogenesis, inter-organelle lipid transfer and lipid droplet degradation are all mediated through them. For example, lipid droplets are synthesised at the endoplasmic reticulum (ER) via direct membrane contact sites. A recent study highlighted the importance of multi-organelle interactions, including those involving lipid droplets, in the metabolic adaptation of the inflammatory response in immune cells. While lipid droplet-organelle contacts are key in many physiological processes, it remains unknown how these contacts change with age or with interventions that induce longevity, especially in a whole-organism context. We characterise changes in the organelle interaction landscape with age, focusing on lipid droplets, and investigate how it differs in long-lived individuals. To this end, we use strains that carry organelle markers, which we track across the animals' lifespans using super-resolution microscopy. In addition, we use protein engineering to identify key factors that mediate organelle interactions during ageing and in long-lived individuals. Importantly, we also explore whether manipulating organelle interactions can extend lifespan or reduce longevity by using genetic perturbations coupled with lifespan studies.

FUTURE DIRECTIONS

Future work will continue to mechanistically unravel the molecular pathways that are driven by beneficial lipids such as MUFAs and lipid storage organelles. We will use genetic perturbations coupled with mass spectrometry and organelle tracking to understand how lipid metabolism protects cells. In conclusion, we are aiming to enhance our understanding of lipid-driven processes during ageing to potentially open new avenues for using lipids as ageing interventions.



▲ **Figure 1**

Strategies to study how monounsaturated fatty acids and lipid droplets extend lifespan. Adapted from Papsdorf *et al.*, *Nat Cell Biol*, 2023 and Biorender.com.

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Silva-García CG, Láscarez-Lagunas LI, Papsdorf K, Heintz C, Prabhakar A, Morrow CS, Pajuelo Torres L, Sharma A, Liu J, Colaiácovo MP, Brunet A and Mair WB (2023) The CRTC-1 transcriptional domain is required for COMPASS complex-mediated longevity in *C. elegans*. *Nat Aging*, 3:1358–1371

Vassilis **Roukos**

> We develop sequencing methods to study when, where & why chromosomes break.

POSITIONS HELD

Since 2022 Affiliated Group Leader, Institute of Molecular Biology (IMB), Mainz

Assistant Professor, Medical School, University of Patras

2015 – 2022 Group Leader, Institute of Molecular Biology (IMB), Mainz

2013 – 2014 NIH Research Fellow, National Cancer Institute, National Institutes of Health (NIH), Bethesda

2008 – 2013 Postdoc, National Cancer Institute, National Institutes of Health (NIH), Bethesda

EDUCATION

2008 PhD in Molecular Biology & Cytogenetics, University of Patras Medical School

2005 MSc in Applications in Medical Sciences, University of Patras Medical School

2002 BSc in Biology, University of Patras

GROUP MEMBERS

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PhD Student Gabriel Longo

DISCOVER MORE

OVERVIEW

The focus of our lab is to understand how cells maintain the integrity of their genomes in the context of 3D genome organisation. We are particularly interested in the life cycle of DNA double-strand breaks (DSBs), very dangerous lesions that, if not faithfully repaired, can lead to cell death or the formation of tumorigenic genome rearrangements. DSBs can be evoked exogenously upon cancer treatment or the use of programmed nucleases such as CRISPR/Cas9, both of which have important clinical implications, or upon the perturbation of intrinsic fundamental cellular processes such as DNA replication and transcription. A central focus of our work is to understand when, where, why and how chromosomes break across the 3D genome, and to understand how these fragile DNA sites can be turned into persistent breaks that promote the formation of genomic rearrangements. Moreover, we are interested in understanding how programmed nucleases, such as Cas9 and Cas12, generate specific cleavage patterns at different locations across the genome and harness this information to increase the fidelity, precision and predictability of genome editing.

RESEARCH HIGHLIGHTS

Linking CRISPR-Cas9 double-strand break profiles to gene editing precision with BreakTag

CRISPR/Cas9 is a powerful genome-editing platform with immense potential for facilitating gene therapy to treat various diseases. However, Cas9 has a flexible scission profile, which might impact repair outcomes, and it is largely unknown what dictates the type of Cas9 incision that is made. We have developed a sensitive, fast, scalable and cleavage pattern-aware methodology named BreakTag to profile CRISPR/Cas9 on and off-target DSBs, which can be used to identify the determinants of Cas9 incisions. We have found that the target sequence determines how Cas9 cleaves DNA and that the type of incision made is strongly associated with the repair outcome. Moreover, we identified Cas9 variants with altered scission profiles and demonstrated that human genetic variation influences

Cas9 cleavage and the editing outcome, suggesting that patients' genetic backgrounds must be taken into consideration before clinically relevant efforts. Our work illuminates the fundamental characteristics of the Cas9 nuclease and lays the foundation for harnessing the flexible cutting profiles of Cas9 and engineered variants for template-free, precise and personalised genome editing (Longo, Sayols *et al.*, 2025, *Nat Biotech*; Figure 1).

Type II topoisomerases shape multi-scale 3D chromatin folding in regions of positive supercoils

Type II topoisomerases (TOP2s) resolve torsional stress accumulated during various cellular processes and are enriched at chromatin loop anchors and topologically associated domain (TAD) boundaries, where they, if trapped, can lead to genomic instability, promoting the formation of oncogenic fusions (Gothe *et al.*, 2019, *Mol Cell*). Whether TOP2s relieve topological constraints at these positions and/or participate in 3D chromosome folding remains unclear. To address this question, we have combined 3D genomics, imaging and GapRUN, a method for genome-wide profiling of positive supercoiling, to assess the role of TOP2s in shaping chromosome organisation in human cells. Our work showed that acute TOP2 depletion led to the emergence of new, large-scale contacts at the boundaries between active, positively supercoiled and lamina-associated domains. TOP2-dependent changes in higher-order chromatin folding were accompanied by remodelling of chromatin-nuclear lamina interactions and gene expression changes, while at the chromatin loop level, TOP2 depletion predominantly remodelled transcriptionally-anchored, positively supercoiled loops. We propose that TOP2s act as a fine-regulator of chromosome folding at multiple scales (Longo *et al.*, 2024, *Mol Cell*).

FUTURE DIRECTIONS

Central to our focus is shedding light on cellular events that promote DNA fragility, either intrinsically or upon treatment with cancer therapy and the use of programmed genome-editing nucleases such as CRISPR/Cas9. In one of our future directions, we intend to profile endogenous DNA breaks across the genome in various cell types, with the aim of identifying common or cell type-specific signatures of DNA fragility. We will then focus on identifying mechanistically how these endogenous DNA breaks form and evaluate how DNA break repair efficiency is influenced by their genomic, chromatin and chromosome organisation context. These studies will directly highlight the link between cell type-specific DNA fragility and repair in the formation of tissue-specific, recurrent oncogenic translocations. In a different direction, we will perform directed evolution and saturation mutagenesis experiments to engineer novel Cas9 variants with higher specificity and predictable editing and will identify the factors that determine the incisions made by other Cas9 nucleases, such as Cas12.

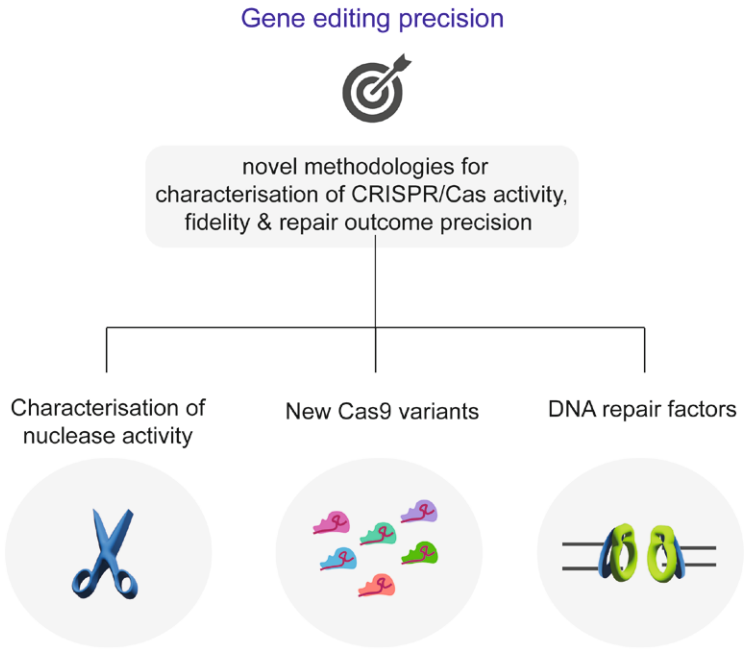

Figure 1

We have developed methods for characterisation of nuclease activity, fidelity and editing outcome, which we will use to identify novel nuclease variants and manipulate repair pathways to increase genome editing predictability and precision.

SELECTED PUBLICATIONS

Longo GMC*, Sayols S*, Kotini AG, Heinen S, Möckel MM, Beli P and Roukos V (2025) Linking CRISPR-Cas9 double-strand break profiles to gene editing precision with BreakTag. *Nat Biotechnol*, 43:608-622

Longo GMC*#, Sayols S* and Roukos V# (2025) Multi-level characterization of genome editor's nuclease activity with BreakTag. *Nat Protoc*, doi: 10.1038/s41596-025-01271-4

Longo GMC*, Sayols S*, Stefanova ME*, Xie T*, Elsayed W*, Panagi A, Stavridou AI, Petrosino G, Ing-Simmons E, Souto Melo U, Gothe HJ, Vaquerizas JM, Kotini AG, Papantonis A#, Mundlos S# and Roukos V# (2024) Type II topoisomerases shape multi-scale 3D chromatin folding in regions of positive supercoils. *Mol Cell*, 84:4267-4281.e8

*indicates joint contribution, #indicates joint correspondence

Sandra **Schick**

> We study how BAF chromatin remodellers regulate our genome to control cell fate.

POSITIONS HELD

Since 2020 Group Leader, Institute of Molecular Biology (IMB), Mainz

2016 – 2020 Postdoctoral Fellow, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna

EDUCATION

2016 PhD in Molecular Biology, Institute of Molecular Biology (IMB), Mainz

2012 MSc in Biomedicine and Diplom in Biology, Johannes Gutenberg University Mainz (JGU)

2008 BSc in Molecular Biology, Johannes Gutenberg University Mainz (JGU)

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Master's Students Thérèsa Koppel, Julia Ziegler

Research Assistant Mara Wolf

Student Assistants Jonas Hahn, Amy-Sue Sattler

*indicates joint PhD students

DISCOVER MORE

OVERVIEW

The condensation of the genome into higher-order chromatin structures requires various dynamic regulatory mechanisms that control the spatiotemporal organisation of genomic processes. These regulatory mechanisms ensure proper gene expression and as such the appropriate execution of all cellular processes. To achieve this, various regulators act in an integrative and coordinated fashion, resulting in a highly complex and fine-tuned system. Therefore, it is not surprising that mutations in genes encoding these regulators are frequently associated with various diseases. To uncover how these regulators integrate and contribute to gene regulation, genome stability and other genomic processes, we employ human cellular model systems and mouse models in combination with genome editing, epigenomics, proteomics and various molecular and biochemical approaches. Moreover, we explore the cellular and molecular consequences of mutations in these regulators to unravel the mechanisms underlying diseases and identify potential therapeutic approaches.

RESEARCH HIGHLIGHTS

One class of chromatin regulators that is essential for modulating chromatin structure is the BRG1/BRM-associated factor (BAF) chromatin remodellers, also known as the mammalian SWI/SNF complexes. These remodellers are polymorphic complexes comprised of multiple subunits that are encoded by around 30 genes and assembled in a combinatorial fashion. There are three subtypes of BAF complexes, each with a few distinct subunits: the canonical BAF complexes (BAF/cBAF), the polybromo-associated BAF complexes (PBAF) and the non-canonical GLTSCR1/1L-BAF complexes (GBAF/ncBAF). These remodellers utilise energy from ATP hydrolysis to slide or eject nucleosomes and thereby modulate DNA accessibility. They control gene regulatory regions and consequently regulate a multitude of cellular functions. They are also crucial for developmental processes such as lineage specification and differentiation. Moreover, BAF complexes contribute to genomic processes such

as the DNA damage response, DNA replication and sister chromatid cohesion, as well as chromatin topology and organisation. The unexpectedly high mutation rate in genes encoding various BAF subunits in cancer and neurodevelopmental disorders further highlights the importance of these remodellers. Therefore, it is of great relevance to elucidate the functions of the diverse BAF complexes and the molecular consequences of mutations in genes encoding BAF complex subunits. These insights will likely enable the development of new targeted therapeutics for BAF-associated diseases.

To achieve this, we systematically investigate the role of distinct BAF complexes in different cellular processes in conventional cell lines using a wide variety of experimental approaches, ranging from live-cell and super-resolution microscopy to genomics and proteomics. Using these approaches, we observe BAF subtype-specific regulatory mechanisms, sometimes with opposing effects. Individual BAF subunits also show unique genome stability-related functions.

In addition, we have established human organoid cultures that closely reflect the development and cellular heterogeneity of organs. These models allow us to investigate the role of BAF complexes in more physiological settings and to unravel their cell type-specific roles. For example, it has been shown that their composition and function can differ by cell type and changes during development. In addition, these models offer a great opportunity to study diseases that are caused by mutations in BAF complex-encoding genes at the molecular and cellular level *in vitro*. Here, our studies show time- and cell type-dependent phenotypic, cellular and molecular alterations following BAF perturbations, which may mimic disease-related alterations in patients with BAF mutations. In particular, developmental processes and tissue homeostasis are impaired, leading, for example, to altered cell composition and function. Apart from this, we use mouse models to study the role of BAF complexes in specific cell types and explore alterations during ageing that may promote age-related disorders.

FUTURE DIRECTIONS

We will further explore the molecular function and regulation of BAF complex subtypes and subunits, the processes they are involved in and how they integrate with other regulatory mechanisms using a number of different experimental and computational approaches. We will also continue to study context-dependent functions of BAF complexes, including their role in developmental processes, disease and ageing. For example, we will systematically explore the role of different BAF complex subunits in brain development and how their disruption by mutations results in neurodevelopmental disorders. Ultimately, our research aims to unravel pathogenic mechanisms that can be targeted for therapy.

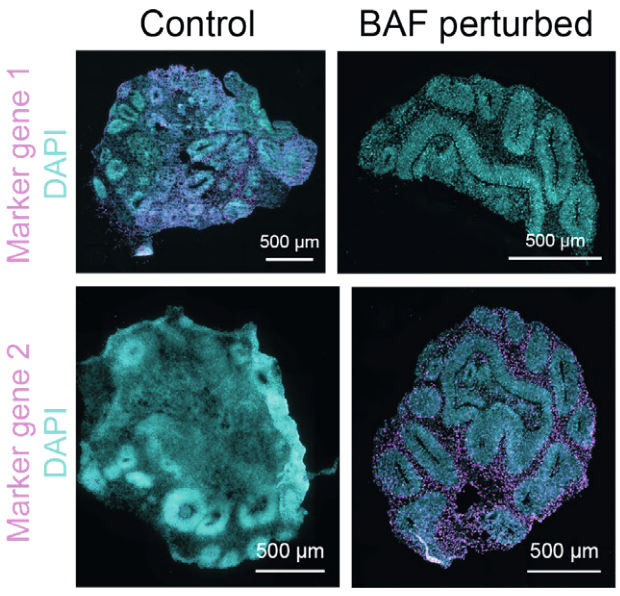

Figure 1

BAF perturbation results in altered cellular fate. Single-cell analyses revealed changes in the cellular composition of brain organoids following BAF perturbation. These findings were confirmed by immunofluorescence staining of the respective marker genes (purple). DNA was stained with DAPI (cyan).

SELECTED PUBLICATIONS

Nguyen TT, Baumann P, Tüscher O, Schick S and Endres K (2023) The aging enteric nervous system. *Int J Mol Sci*, 24:9471

Schick S*#, Grosche S*, Kohl KE*, Drpic D, Jaeger MG, Marella NC, Imrichova H, Lin JMG, Hofstätter G, Schuster M, Rendeiro AF, Koren A, Petronczki M, Bock C, Müller AC, Winter GE and Kubicek S# (2021) Acute BAF perturbation causes immediate changes in chromatin accessibility. *Nat Genet*, 53:269–278

Varga J, Kube M, Luck K and Schick S (2021) The BAF chromatin remodeling complexes: structure, function, and synthetic lethalities. *Biochem Soc Trans*, 49:1489–1503

*indicates joint contribution, #indicates joint correspondence

Lukas **Stelzl**

> We use multi-scale simulations of biomolecules to understand how dynamic self-organisation regulates genes.

POSITIONS HELD

Since 2024	Adjunct Director, Institute of Molecular Biology (IMB), Mainz
	Professor of Biomolecular Simulations, Johannes Gutenberg University Mainz (JGU)
2020 – 2024	Adjunct Group Leader, Institute of Molecular Biology (IMB), Mainz
	ReALity Junior Group Leader, Johannes Gutenberg University Mainz
2015 – 2020	Postdoctoral Fellow, Max Planck Institute of Biophysics, Frankfurt am Main

EDUCATION

2015	PhD in Biochemistry, University of Oxford
2010	MSc in Molecular and Cellular Biochemistry, University of Oxford

GROUP MEMBERS

Postdoc Arya Changiarath Sivadasan

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Master's Students Lilia Marks Braun, Christian Fabri, Stefan Grünewald-Borras

Student Assistants Leon Persch, Dennis Martin, Minoo Rostami, Rebecca Ziora

DISCOVER MORE

OVERVIEW

We aim to elucidate how liquid-liquid phase separation and phase-separated condensates of proteins and nucleic acids provide specific regulation and how this is lost in pathologies. We are a computational group that uses chemically detailed multi-scale simulations of biomolecules in our research (Gaurav *et al.*, 2025, *Biophys J*; Stelzl *et al.*, 2020, *eLife*; Stelzl* & Pietrek*, 2022, *JACS Au*), bridging atomic-resolution simulations to phase-separated condensates (Grujis da Silva *et al.*, 2022, *EMBO J*). Phase separation organises biological functions in time and space. Thus, it not only plays an important role in regulating genes at the transcriptional level, but also at the post-transcriptional level. Dysregulation of liquid-liquid phase separation is hypothesised to be an important driver of ageing and age-related diseases.

Recently, we have shown how ATP-driven enzymatic phosphorylation can modulate and control condensation of proteins (Zippo *et al.*, 2025, *Nat Commun*). Using simulations, we can also start to learn patterns that determine the interactions of proteins with condensates (Changiarath *et al.*, 2025, *Faraday Discuss*).

RESEARCH HIGHLIGHTS

With Dorothee Dormann (IMB/JGU), we study TDP-43 phosphorylation, which is a hallmark of neurodegenerative disease. We are elucidating how interactions between different parts of TDP-43 shape its behaviour and how they are influenced by disease-linked phosphorylation. Recently, we developed a new simulation method to study ATP-driven processes in cells (as part of the CRC/TRR 146; Zippo *et al.*, 2025, *Nat Commun*) and demonstrated how TDP-43 is enzymatically phosphorylated by casein kinase 1 δ (Ck1d). Previously, it was not known whether TDP-43 is only phosphorylated as a dilute solution or whether it can also be phosphorylated in condensates. Our simulations demonstrate that enzymatic phosphorylation happens preferably at the interface of the condensate with the aqueous solution, where there are many attractive interactions anchoring the condensates and many potential substrate Ser

sites for the kinase. In the simulations, TDP-43 condensates dissolve as they become phosphorylated (Figure 1), suggesting that sequence patterning rather than sequence position determines which residues are the most readily phosphorylated.

With Jan Padeken (IMB), we showed that the RNA polymerase II C-terminal domain (CTD) forms distinct condensates to regulate transcription initiation and elongation (Changiarath *et al.*, 2024, *bioRxiv*). In simulations, phosphorylation of the RNA polymerase II CTD triggered the formation of two distinct condensates for transcription initiation and elongation, respectively, which could underpin differential recruitment of transcription machinery components. We identified Pro-Tyr interactions (Flores-Solis *et al.*, 2023, *Nat Comm*), which may be important for recruiting the Mediator complex to the CTD phase for transcription initiation. Intriguingly, the condensate phase of unphosphorylated CTD is fully and partially engulfed by condensates of phosphorylated CTD and elongation factors. Super-resolution microscopy in *C. elegans* by Jan Padeken confirmed the existence of these multi-phasic condensates. We trained a neural network on simulations of CTD condensates with different proteins (Changiarath *et al.*, 2024, *Faraday Discuss*) to identify residues that interact with the CTD. Based on this, we inverted the morphology of CTD condensates. We asked the neural network to design suitable peptides and investigated them in simulations. The results were fed into the neural network, which predicted that heterochromatin-associated protein sequences identified by the Padeken lab interact poorly with the CTD. This shows how combining molecular dynamics and neural networks can provide biologically meaningful insights.

Our simulations also predicted that CTD condensates would be more stable at higher temperatures, which is the opposite of most protein condensates. *In vivo* experiments by the Padeken lab supported our simulations and showed that gene expression is modulated as a result. Taken together, this may explain how CTD condensates can regulate different biological processes.

Together with the Ketting lab (in CRC 1551), we are elucidating how different phase-separated condensates specifically recruit proteins. Mutator foci are essential for small RNA biology in *C. elegans* and for suppressing transposable elements. To do this, they recruit proteins with the scaffold protein Mut-16. Mut-16 recruits Rde-2/Mut-7, but how Rde-2 binds to Mut-16 is not understood. Using multi-scale simulations, we resolved how the disordered prion-like domain of Rde-2 binds Mut-16 condensates at atomic resolution (Gaurav *et al.*, 2024, *Biophys J*). Simulations highlighted specific Arg residues that were also found to be important in *in vitro* experiments. Subsequent experiments showed that our simulations correctly predicted the phase separation propensities of different MUT-16 regions.

FUTURE DIRECTIONS

We will continue to develop simulation methods to improve our models and better match experimental complexity. The group is also part of the CRC 1552 on "Molecular defects in soft matter" and RTG 2516 on "Control of structure formation in soft matter at and through interfaces", where we focus on the recognition of PTMs and small molecules by proteins and the control of dynamic self-organisation as applied to artificial DNA-based transmembrane receptors. We are also part of the Carl Zeiss Centre MAINCE, where we are combining simulations with neural networks to understand on- and off-target interactions of small molecules with complex mixtures of proteins. Longer term, our simulation methods will be vital for understanding cellular homeostasis, including the proper functioning of phase-separated condensates. In the future, we will combine molecular dynamics simulations and neural networks to understand the principles of dynamic self-organisation and how these underpin biological function.

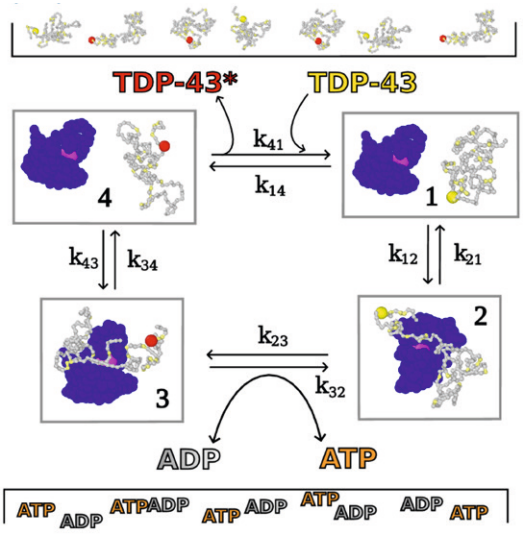

Figure 1

Enzymatic phosphorylation cycle driven by ATP consumption. In state 1, TDP-43 (gray) is unphosphorylated and not bound to the kinase CK1δ (blue, active site in pink). In state 2, TDP-43 binds to CK1δ. In state 3, the reactive serine is phosphorylated by the kinase, converting one ATP into one ADP. In state 4, phosphorylated TDP-43 dissociates from CK1δ. Phosphorylated and unphosphorylated TDP-43 are supplied through reservoirs, and we considered exchanges between these reservoirs and our simulation box. Serines are in yellow, while phospho-serines are in red. From Zippo *et al.*, 2025, *Nat Commun*.

SELECTED PUBLICATIONS

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Stelzl LS*, Pietrek LM*, Holla A, Oroz J, Sikora M, Köfinger J, Schuler B, Zweckstetter M and Hummer G (2022) Global structure of the intrinsically disordered protein Tau emerges from its local structure. *JACS Au*, 2:673–686

*indicates joint contribution

Helle **Ulrich**

> Chromatin remodelling supports DNA lesion processing during genome replication.

POSITIONS HELD

Since 2013 Scientific Director, Institute of Molecular Biology (IMB), Mainz
Professor, Johannes Gutenberg University Mainz (JGU)
2004 – 2012 Group Leader, Clare Hall Laboratories, Cancer Research UK London Research Institute
2000 – 2004 Group Leader, Max Planck Institute for Terrestrial Microbiology, Marburg
1998 – 2000 Postdoc, Max Planck Institute for Biochemistry, Martinsried
1997 – 1998 Postdoc, Centre for Molecular Biology (ZMBH), University of Heidelberg

EDUCATION

2004 Habilitation in Genetics, Philipps University Marburg
1996 PhD in Chemistry, University of California, Berkeley
1994 Diplom in Biology, Georg August University Göttingen

GROUP MEMBERS

Team Leaders Maximilian Reuter, Hans-Peter Wollscheid
Postdocs Katarzyna Maslowska, Cindy Meister, Kirill Petriukov, Christian Renz, Philipp Schönberger, Virender Kumar Sharma, Ronald Wong, Nicola Zilio
PhD Students Kezia Ann, Nadia Da Silva Fernandes*, Yael Hartig, Wiktoria Kabza, Yogita Mallu Kattimani*, Nils Krapoth, Oliver Ordowski, Chitra Roy, Aina Mas Sanchez*, Markus Schraft, Felizitas Stiehler, Abhik Thapa
Master's Student Vanessa Rauthe
Bachelor's Students Majd Hadji, Anne Söding
Lab Manager Ulrike Seeburg
Technicians Julia Jager, Violeta Morin
Student Assistant Lia Willerding
Personal Assistant Jutta Karn

*indicates joint PhD students

DISCOVER MORE

OVERVIEW

A robust response to DNA replication stress is an important defence mechanism against genome instability and serves as a last barrier against the development of cancer. Our lab studies the regulatory mechanisms that contribute to ensuring the complete and accurate duplication of a cell's genetic information in every cell cycle, especially as they relate to the posttranslational protein modifiers ubiquitin and SUMO. We aim to understand how cells choose between alternative processing pathways for replication-blocking lesions in the DNA template, for example between error-prone translesion synthesis and accurate recombination-mediated template switching, or between fork-associated and postreplicative modes of DNA damage bypass. Posttranslational modifications of the replication clamp protein PCNA by mono- and polyubiquitylation have proven to be critical determinants of this pathway in eukaryotes. Over the past years, we have addressed the question of how the pathway of DNA damage bypass, controlled by the ubiquitylation of PCNA, is modulated in the context of chromatin.

RESEARCH HIGHLIGHTS

DNA damage bypass operates at least in part in a postreplicative manner via replication repriming downstream of lesions. This process gives rise to so-called daughter-strand gaps that activate damage signalling and are filled by the ubiquitin-dependent damage bypass system independently of the replisome. Considering that newly synthesised DNA is rapidly chromatinised after the passage of the replisome, daughter-strand gap filling is therefore likely to occur in a chromatin environment. Yet, the influence of chromatin on DNA damage bypass is still poorly understood. Chromatin structure and dynamics are regulated at multiple levels by the identities and posttranslational modifications of histones, as well as the positioning, exchange, or removal of nucleosomes by histone chaperones and chromatin remodellers. We have now identified the mechanistic basis for how a conserved chromatin remodeller, the INO80 complex, contributes to DNA damage

bypass. This complex plays diverse roles in transcription, replication and DNA repair, where it mediates nucleosome sliding as well as the exchange of the histone variant H2A.Z from chromatin. In DNA double-strand break repair, the INO80 complex supports homologous recombination. A contribution to DNA damage bypass upstream of PCNA ubiquitylation was postulated in yeast and mammalian cells.

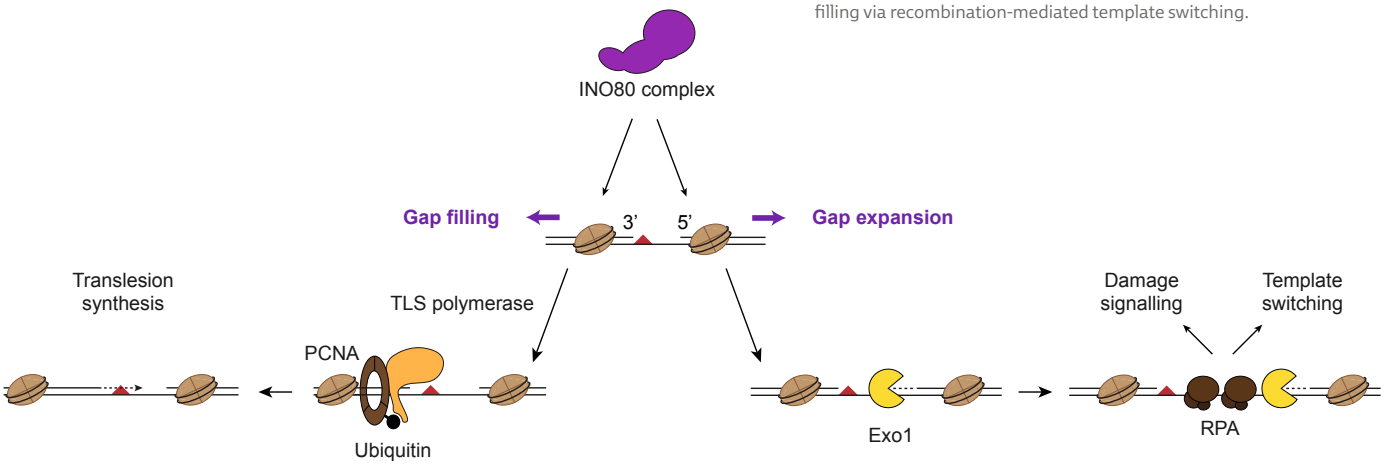
Upon revisiting these findings, we discovered that the INO80 complex acts in DNA damage bypass not upstream, but downstream of PCNA ubiquitylation. By genetically separating the process of lesion bypass from genome replication, we found that the INO80 complex facilitates Exo1-dependent expansion of daughter-strand gaps. At the same time, it also promotes gap filling, resulting in a net contribution to gap repair. Unexpectedly, its function in postreplicative damage bypass was independent of its potential role in H2A.Z exchange and therefore distinct from its action at DNA double-strand breaks. In collaboration with the lab of Karl-Peter Hopfner (LMU Munich), we were able to show that purified, recombinant INO80 complex is able to reposition nucleosomes away from junction structures mimicking both ends of daughter-strand gaps. This finding provides a possible mechanistic explanation for the effects of INO80 on gap expansion and filling, respectively (Figure 1). Our study therefore reveals a novel, H2A.Z-independent function of the INO80 complex in the bypass of DNA lesions that appears to be mediated by its ruler-like activity in nucleosome repositioning around postreplicative daughter-strand gaps.

FUTURE DIRECTIONS

Additional research is clearly needed for better insight into the role of chromatin in lesion processing. On the one hand, it will be important to understand the crosstalk between the INO80 complex and other chromatin remodellers, as well as the effects of epigenetic chromatin modifications that might modulate the accessibility of stalled forks or daughter-strand gaps. Accordingly, a variety of chromatin-regulatory factors have been implicated genetically in DNA damage bypass without a mechanistic basis. On the other hand, daughter-strand gaps are emerging as widespread, but fragile intermediates of DNA damage processing during genome replication. These structures have been proposed to underlie the sensitivity of BRCA-deficient tumour cells to inhibitors of homologous recombination, underlining their clinical relevance. Yet, their basic characteristics, including their genome-wide distribution, length and their strand bias, are poorly understood, and their importance relative to the much better-characterised stalled replication forks is still debated. To address this knowledge gap, we plan to develop tools for the genome-wide mapping and molecular characterisation of daughter-strand gaps.

▼ Figure 1

Model of how the INO80 complex contributes to postreplicative DNA damage bypass. By repositioning nucleosomes away from the boundaries of daughter-strand gaps, the INO80 complex can enhance access to the 3′-terminus of the junction, thus promoting translesion synthesis. Alternatively, enhanced access to the 5′-terminus of the junction facilitates damage bypass by initial gap expansion via Exo1-mediated resection, which in turn promotes checkpoint activation and subsequent gap filling via recombination-mediated template switching.



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Renz C, Asimaki E, Meister C, Albanèse V, Petriukov K, Krapoth NC, Wegmann S, Wollscheid HP, Wong RP, Fulzele A, Chen JX, Léon S and Ulrich HD (2024) Ubiquiton – an inducible, linkage-specific polyubiquitylation tool. *Mol Cell*, 84:386–400

Wegmann S*, Meister C*, Renz C, Yakoub G, Wollscheid HP, Takahashi DT, Mikicic I, Beli P and Ulrich HD (2022) Linkage reprogramming by tailor-made E3s reveals polyubiquitin chain requirements in DNA damage bypass. *Mol Cell*, 82:1589–1602.e5

*indicates joint contribution

Sara **Vieira-Silva**

> We examine microbial populations in the human gut to assess their impact on disease & therapeutic outcomes.

POSITIONS HELD

Since 2022	Adjunct Director, Institute of Molecular Biology (IMB), Mainz
	Professor, University Medical Center, Johannes Gutenberg University Mainz (JGU)
2022	Group Leader, University Medical Center, Johannes Gutenberg University Mainz (JGU)
2015 – 2022	Postdoc, Catholic University of Leuven (KU Leuven)
2011 – 2015	Postdoc, Free University of Brussels

EDUCATION

2007 – 2010	PhD in Genomics, Pierre and Marie Curie University/Institut Pasteur, Paris
2005 – 2006	Postgraduate studies in Computational Biology (PDBC), Instituto Gulbenkian de Ciência, Oeiras
2003	Diploma in Biology, University of Lisbon (FCUL)

GROUP MEMBERS

Postdoc Anna Lambert

PhD Students Javier Centelles-Lodeiro, Bharat Joshi, Laura Peschke

DISCOVER MORE

OVERVIEW

The human body hosts microbial communities that play an essential role in maintaining health. My group focuses on elucidating the ecological dynamics of human gut-associated microbial communities in sustaining host-microbiome homeostasis and how their disruption contributes to the risk of disease onset or progression. We employ quantitative approaches in population cohorts and intervention trials to identify the mechanisms that govern gut ecosystem dynamics in health, the factors that determine its resilience to perturbations, and the specific alterations that drive disease and/or influence therapeutic success or failure. We concentrate on characterising the metabolic capacity of these complex communities and their symbiotic or deleterious interactions with the host and its immune system. Our overarching objective is to define and quantify the contribution of gut microbiome perturbations to the risk of disease development and to support the advancement of strategies for microbiota remediation as part of therapeutic interventions. To this end, we emphasise hypothesis-driven experimental design and invest in developing experimental and computational methodologies to study human-associated microbial communities.

RESEARCH HIGHLIGHTS

How to refine microbiota modulation strategies for the treatment of chronic inflammatory disease

Inflammatory bowel disease (IBD) encompasses complex disorders of the gastrointestinal tract that are driven by immune responses to environmental factors, often in genetically susceptible individuals. The gut microbiota acts both as an immune modulator and a contributing environmental trigger. In a large longitudinal cohort of patients undergoing treatment with biological immune modulators, we used quantitative microbiota profiling to assess how microbial alterations vary with disease presentation and medication. We identified opportunistic bacteria whose abundance correlated with inflammation and its reduction during therapy, suggesting a role in treatment failure. In collaboration with partners at KU Leuven

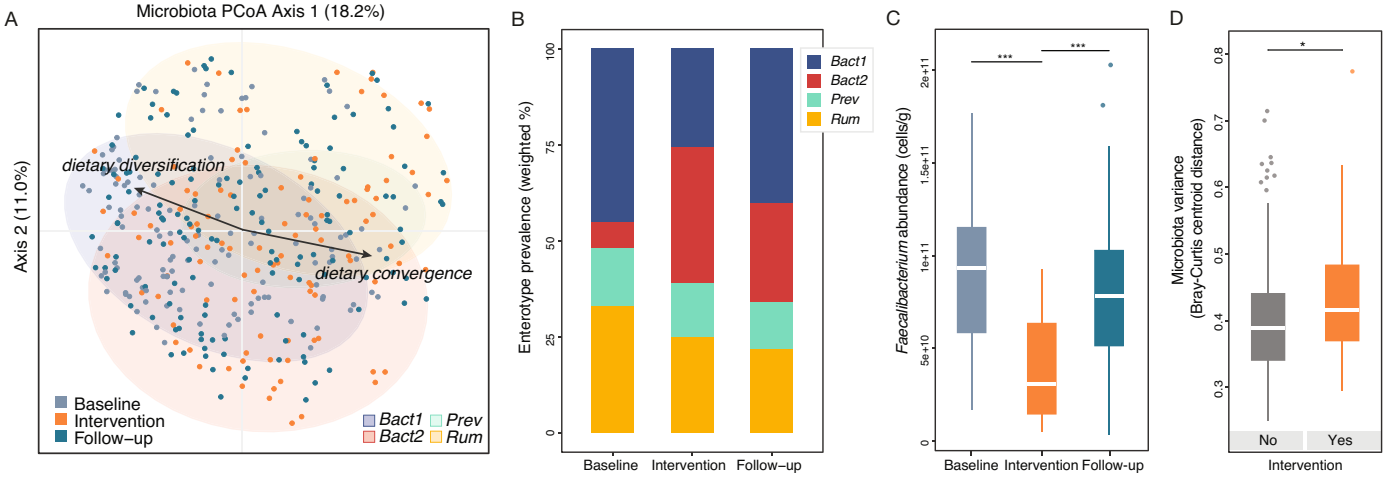
(Belgium), we are using microbiome information to devise personalised medicine approaches through stratification or combined intervention. Patient stratification for optimal treatment was tackled by developing machine learning models that integrate clinical and microbiota-derived features to predict therapeutic responses for multiple therapeutic choices. Combined intervention on the microbiota as well as inflammation is an opportunity to rescue non-responders. We are tackling the optimisation and refinement of protocols for faecal microbiota transplantation as a microbiota restoration strategy, by testing intervention success in rigorous designs with quantitative data generation.

How to modulate the human gut microbiome through dietary intervention

Dietary variation has been identified as a key contributor to gut microbiome diversification, sustaining its role in human health. While a multitude of dietary interventions have been suggested to positively impact human physiology and/or the microbiome, here we designed a study to examine the effects of reduced dietary variation on gut microbiota composition in healthy adults who usually consumed a Western-type diet. Short-term restriction to a simplified diet (restricted in type of macronutrients, without caloric restriction) altered specific community features. Notably, a simplified diet reduced microbial load and *Faecalibacterium* abundance – an essential symbiont for human-microbiome homeostasis – and increased the prevalence of a Bacteroides-dominated community type, which is typically associated with chronic inflammation. These shifts were temporary, with volunteers recovering after returning to their normal diet. Additionally, despite this extremely restricted dietary convergence, the gut microbial communities did not converge across individuals, and there was substantial interindividual variability in the degree of impact of the intervention (Figure 1). These findings indicate that dietary restriction has a temporary negative impact on gut microbiome composition. Dietary convergence does influence gut microbiome composition, but may be insufficient to drive a uniform response.

FUTURE DIRECTIONS

Our group continues to devise new approaches to study the role of human gut microbiota in health and its perturbation as a potential risk factor for increased disease susceptibility throughout life. We aim to uncover how gut microbiota composition modulates therapeutic efficacy and patient outcomes in order to devise new remediation approaches for personalised medicine.



▲ **Figure 1**

Dietary convergence induces individual responses in faecal microbiome composition (adapted from Vermeulen *et al.*, 2025). A) Visualisation of the impact of dietary convergence on the gut microbiome, pushing communities towards the pro-inflammatory enterotype Bact2, which increases in prevalence but recovers after the intervention is suspended (B). C) *Faecalibacterium*, an essential commensal for gut homeostasis, is similarly drastically but temporarily impacted. D) Microbiome composition across individuals does not converge with dietary convergence.

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Caenepeel C*, Falony G*, Machiels K, Verstockt B, Goncalves PJ, Ferrante M, Sabino J, Raes J°, Vieira-Silva S° and Vermeire S° (2024) Dysbiosis and associated stool features improve prediction of response to biological therapy in inflammatory bowel disease. *Gastroenterology*, 166:483–495

Valles-Colomer M*, Bacigalupe R*, Vieira-Silva S*, Suzuki S, Darzi Y, Tito RY, Yamada T, Segata N, Raes J° and Falony G° (2022) Variation and transmission of the human gut microbiota across multiple familial generations. *Nat Microbiol*, 7:87–96

*indicates joint contribution, °indicates joint senior author

Siyao **Wang**

> We study the role of epigenetics in the long-term DNA damage response.

POSITIONS HELD

Since 2023 Group Leader, Institute of Molecular Biology (IMB), Mainz

Since 2022 Group Leader, Institute for Genome Stability in Ageing and Disease (IGSAD), University Hospital of Cologne

2015 – 2022 Postdoc, CECAD, University Hospital of Cologne

EDUCATION

2015 PhD in Molecular Cancer, University of Manchester

2010 BMed in Preclinical Medicine, Southern Medical University, Guangzhou

GROUP MEMBERS

PhD Students Rose Mary Roshan, Jóhann Örn Thorarensen

Master's Students Amy-Sue Sattler, Nadine Spiegler

Lab Technicians Neda Bakhshandeh, Annie-Kermen Boromangnaeva

Student Assistants Sultan Zara Ates, Ria Shah, Negin Yazani

DISCOVER MORE

OVERVIEW

DNA damage poses a major threat to genome stability, chromosomal integrity and cellular function. Defects in transcription-coupled nucleotide excision repair (TC-NER) cause growth and mental retardation, photosensitivity and premature ageing in Cockayne syndrome (CS) patients. To ensure the success of DNA repair, chromatin serves as a platform and is dynamically changed during the DNA damage response (DDR), as described by the Access-Repair-Restore model. As a crucial part of chromatin, histones are post-translationally modified via methylation, ubiquitination and acetylation to regulate DDR-related chromatin functions. Importantly, in contrast to the transient process of DNA repair, many histone modifications can leave a long-term epigenetic memory in cells and be passed down to further generations, raising the question of whether DNA damage could reshape the epigenome in damaged cells and even affect their descendants. My lab uses *C. elegans* as a model to study the role of histone modifications in genome stability, longevity and transgenerational inheritance.

RESEARCH HIGHLIGHTS

Transgenerational inheritance of paternal DNA damage via histone-mediated DNA repair restriction

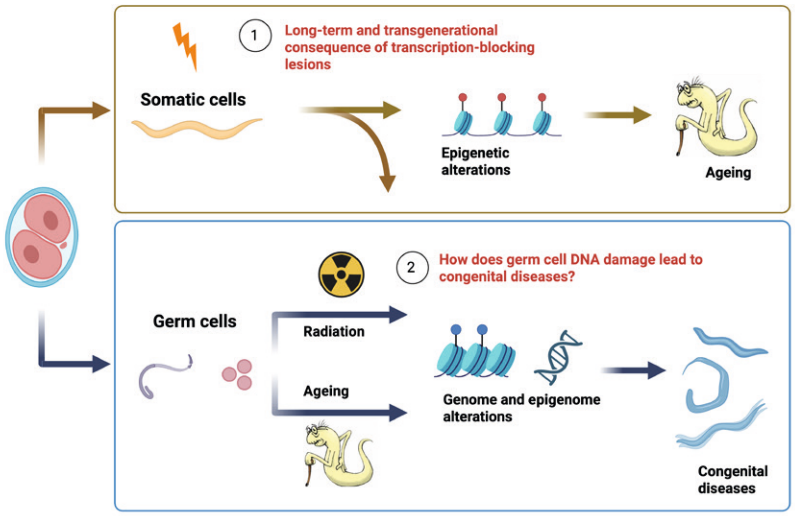
Epigenetic modifications are well-known for their role in the transgenerational inheritance of several traits, including longevity. However, whether DNA damage-induced epigenetic alterations can lead to a transgenerational effect is unknown. The transgenerational effect of DNA damage was previously studied, mainly via epidemiological and genetic approaches, with contradictory results. Interestingly, many studies pointed to the hypothesis that the transgenerational effect is attributed to paternal, but not maternal, DNA damage, although the mechanism underlying this phenomenon was unclear.

Previously, I identified a novel mechanism underlying the transgenerational genetic and epigenetic effects of paternal DNA damage. Using sex-separated *C. elegans* strains, we found that

paternal but not maternal ionising radiation (IR) exposure leads to transgenerational embryonic lethality. We also determined that IR-induced paternal DNA double-strand breaks (DSBs) are mainly repaired via maternally-provided error-prone polymerase-theta mediated end joining (TMEJ), while maternal DNA DSBs mainly engage in error-free homologous recombination repair (HRR). Consequently, offspring of irradiated males display genome instability phenotypes, including chromosomal bridging, chromosomal lagging and DNA fragmentation. Our current work aims to determine how DNA polymerase theta (POLQ-1) engages in repairing paternal DNA damage. Specifically, we are investigating the impact of chromatin modifications and chromatin architecture on POLQ-1-mediated paternal DNA repair. Moreover, this persistent paternal DNA damage in the offspring can lead to long-term genomic instability across generations. We used omics technologies to identify the long-term consequences of paternal DNA damage on the proteome, transcriptome and genome. Importantly, we study the molecular mechanism underlying physiological outcomes such as longevity, fertility and behavioural changes. Overall, this work identified a novel mechanism for the transgenerational inheritance of paternal DNA damage and provided a potential therapeutic target for improving the progeny viability of patients treated with radiotherapy.

H3K4me2 regulates the recovery of protein biosynthesis and homeostasis following DNA damage

How DNA damage reshapes the epigenome and influences ageing is a fascinating question. I previously identified a role for histone 3 lysine 4 di-methylation (H3K4me2) in the recovery of protein biosynthesis and homeostasis following UV-induced TC-NER. Upon UV treatment, H3K4me2 deposition is transiently increased in the somatic tissues of *C. elegans*. Blocking H3K4me2 deposition by removing the H3K4 methyltransferase complex MLL/COMPASS resulted in developmental arrest and lifespan shortening after UV treatment. In contrast, elevating H3K4me2 by depleting the histone demethylase SPR-5 can accelerate development and extend lifespan upon UV damage. Specifically, we showed that UV-induced H3K4me2 facilitates the transcriptional recovery of protein biosynthesis and homeostasis genes. In addition, we are investigating chromatin homeostasis in response to UV-induced damage by examining the balance between the active chromatin mark H3K4me2 and the repressive mark H3K9me2. Disruption of this is expected to lead to long-term and heritable physiological consequences, such as developmental delay and lifespan shortening. This study highlights the importance of H3K4me2 in the long-term regulation of development and ageing following transcription-blocking DNA damage.



▲ **Figure 1** Strategies to study the long-term and transgenerational consequences of DNA damage.

FUTURE DIRECTIONS

Our future work will explore the long-term and transgenerational effects of DNA damage on congenital diseases and ageing. Paternal DNA damage is associated with neurological disorders, childhood cancers and other congenital diseases. To understand the molecular mechanisms underlying these diseases, we will monitor genomic, epigenetic and proteomic alterations in different generations following DNA damage. We will characterise the phenotypes of genomic instability in offspring and identify epigenetic regulators that may regulate them. By screening mutants of epigenetic modifiers, we will be able to find potential therapeutic targets for DNA damage-related hereditary disorders.

One of the main reasons for endogenous DNA damage in germ cells is reproductive ageing. We will investigate whether paternal age influences genome stability in offspring. We will use males of different ages as fathers to examine the mutation load and signatures in subsequent generations. We will use state-of-the-art technology to identify rare somatic mutations in the progeny. The aim is to understand the mechanism of age-related heritable diseases.

SELECTED PUBLICATIONS

Wang S, Meyer DH and Schumacher B (2023) Inheritance of paternal DNA damage by histone-mediated repair restriction. *Nature*, 613:365-374

Soltanmohammadi N*, Wang S* and Schumacher B (2022) Somatic PMK-1/p38 signaling links environmental stress to germ cell apoptosis and heritable euploidy. *Nat Commun*, 13:701

Wang S, Meyer DH and Schumacher B (2020) H3K4me2 regulates the recovery of protein biosynthesis and homeostasis following DNA damage. *Nat Struct Mol Biol*, 27:1165-1177

*indicates joint contribution

Sina **Wittmann**

> We want to understand how condensates regulate transcription.

POSITIONS HELD

Since 2023 Group Leader, Institute of Molecular Biology (IMB), Mainz

2017 – 2022 Postdoc, Max Planck Institute of Molecular Cell Biology & Genetics, Dresden

EDUCATION

2017 PhD in Biochemistry, University of Oxford

2012 MSc in Biochemistry, University of Regensburg

2009 BSc in Biochemistry, University of Regensburg

GROUP MEMBERS

Postdoc Elnaz Hosseini

PhD Students Radhika Khatter, Felizitas Stiehler, Leonard Tankred Thews

Lab Technician Franziska Roth

Student Assistants Mia Behrensmeyer, Bernadette Lang, Mahdi Narimani

DISCOVER MORE

OVERVIEW

In my group, we aim to understand the molecular mechanisms by which gene activation is regulated. Many decades of intricate work have identified hundreds of proteins that participate in the gene activation process, as well as what role they play. In contrast to older research that focused on structured protein domains, we focus our attention on intrinsically disordered regions. Structure predictors and AlphaFold have shown that transcriptional proteins are particularly disordered compared to the rest of the proteome. We, therefore, believe that these regions play a major, yet largely unknown, role in the regulation of transcription. In my research group, we are trying to understand how transcriptional proteins use their intrinsically disordered regions to communicate with each other and with the chromatin they bind to. This communication involves the formation of small condensates with liquid-like properties. We can rebuild such condensates on single DNA molecules *in vitro*, which we use to study their formation and biophysically characterise their properties. The knowledge gained helps us to design cellular experiments that are aimed at understanding why transcriptional condensates form in the first place. In the long term, we want to use this knowledge to manipulate cells and gain a better understanding of the function of these transcriptional condensates.

RESEARCH HIGHLIGHTS

Formation of transcriptional condensates on DNA

Gene activation plays a major role during development and needs to be precisely regulated for the correct formation of different cell types. If this regulation breaks down, the cell loses control of its transcriptional programme, which can result in cancerous transitions. Transcription initiation is a complex process that requires a plethora of different transcriptional proteins. Some of them have DNA-binding domains and are recruited via direct interaction with chromatin, others can only bind to chromatin indirectly by interacting with proteins that are bound to the DNA. However, what all these transcriptional proteins have in common are their large, disordered

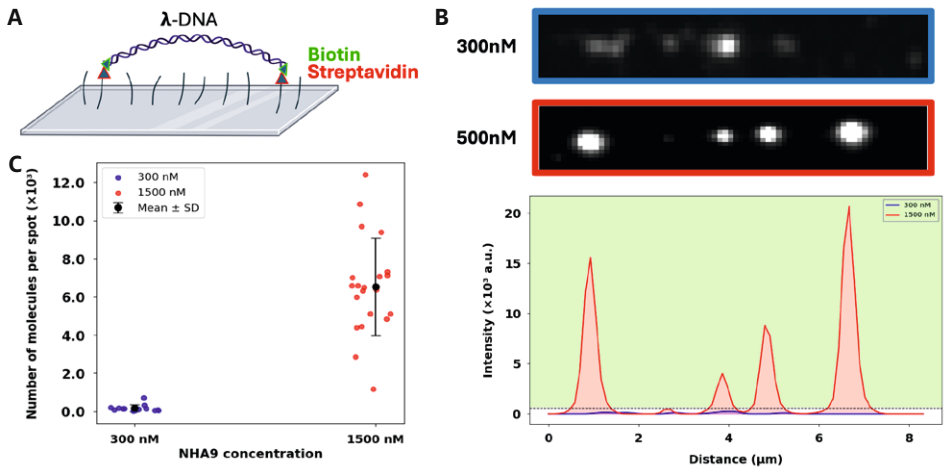
regions, which they use to interact with each other. By doing so, they form small condensates on the DNA that concentrate all the proteins necessary to open up the chromatin and start transcription. The necessity for condensate formation is poorly understood, but previous research indicates that they play a role during development and the stress response, as well as in cancer.

In my past research, we rebuilt such condensates using the DNA-binding transcription factor KLF4 (Krüppel-like factor 4). For this, we utilised single-molecule assays in which individual DNA molecules are tethered on a microscope cover slip. By using fluorescently labelled proteins, this setup allowed us to look at the formation of KLF4 condensates directly on single DNA molecules. From this study, we found that DNA enables these protein condensates to occur at low, physiological KLF4 concentrations and specifically at sites that contain KLF4 recognition motifs. Now, we can show that KLF4 is not the only transcription factor with this ability: we recently found that the oncogenic fusion transcription factor NUP98-HOXA9 also condenses on DNA, demonstrating that our finding is of both general and disease relevance (Figure 1). NUP98-HOXA9 occurs in certain leukaemia types that arise from chromosomal rearrangements fusing the disordered region of NUP98 – a protein completely unrelated to transcription – with the DNA-binding domain of the transcription factor HOXA. This new protein functions as a transcription factor, but without its native intrinsically disordered region the cell cannot regulate it properly. As a result, NUP98-HOXA9 is a very potent driver of oncogenic gene expression and is, as such, responsible for the cancerous transition of leukaemia cells.

FUTURE DIRECTIONS

Going forward, we also want to test condensation in other contexts that are of physiological relevance. For example, our previous research only took naked DNA into consideration. However, in the cell DNA is wrapped around a protein complex called the nucleosome, and together they form the chromatin. In the lab, we aim to reconstitute chromatin and will investigate whether it can also serve as a condensation surface. Furthermore, we are extending our transcription factor repertoire and will include several proteins that control cell differentiation during embryonic development. Next, we will test the condensation behaviour of different combinations of these proteins. We are also extending our research to processes that occur after transcription factor binding. For this, we will test whether proteins that interact with transcription factors can be recruited into the condensed phase.

In addition, within the CRC 1551 we are collaborating with other groups to better understand the regulation of gene expression by transcription factors. This includes the use of cellular models (Sandra Schick, IMB), theoretical modelling (Thomas Speck, University of Stuttgart) and microphase separation in solution (Edward Lemke, IMB and Mainz University, as well as Martin Girard, Max Planck Institute for Polymer Research).



▲ **Figure 1**

NHA9 forms condensates on DNA. A) Schematic representation of an experimental setup: DNA from the γ-phage is immobilised on a glass cover slip by biotin-streptavidin interaction. B) Top: Representative microscopic images of NHA9 binding to γ-DNA in the assay shown in A. Bottom: Intensity profile of the images shown above. The green area indicates condensate formation, while binding in the white area corresponds to simple protein adsorption. Two different protein concentrations were used, as indicated. C) Quantification of individual spots shows that a large number of molecules cluster together at high protein concentrations, which would constitute a condensate. However, at low NHA9 concentrations, the number of molecules in every spot is too low to be considered a condensate.

SELECTED PUBLICATIONS

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*indicates joint contribution

ADJUNCT CLINICIANS

Stephan **Grabbe**

> We study the role of of β2 integrins in skin ageing & cancer immunity.

POSITIONS HELD

Since 2022	Adjunct Clinician, Institute of Molecular Biology (IMB), Mainz
Since 2007	Director, Department of Dermatology, University Medical Center (UMC), Mainz
2003 – 2007	Director, Department of Dermatology, University of Essen Medical Center
2000 – 2003	Professor of Dermatology & Dermato-Oncology, University of Münster
1998 – 1999	Heisenberg Scholarship Visiting Scientist, Skin Disease Research Center, Brigham and Women's Hospital, Harvard University, Boston
1992 – 1998	Research Associate, University of Münster
1989 – 1992	Postdoctoral Research Fellow, Wellman Laboratories of Photomedicine and MGH-Harvard Cutaneous Biology Research Center, Massachusetts General Hospital, Harvard University, Boston
1987 – 1989	Research Associate, University of Münster

EDUCATION

1996	Habilitation, University of Münster
1996	Dermatology, Allergology & Phlebology National Boards (Germany)
1987	MD, University of Münster
1987	Medical School, University of Münster

DISCOVER MORE

RESEARCH HIGHLIGHTS

Within my research group, we pursue several aspects of cutaneous and general immunology research. Our projects centre on cellular immunology, with a focus on dendritic cells and regulatory T cells. The group is tightly embedded into two collaborative research centres: the "Nano@liver" consortium, funded by the Carl Zeiss Foundation, on "Nanoparticle-mediated modulation of the liver micromilieu", of which I am the Speaker, and the CRC TRR156 on "The skin immune system", of which I am the Site Coordinator for Mainz. Moreover, we are part of the JGU "Research Center for Immunotherapy (*Forschungszentrum für Immuntherapie*, FZI)" (speakers: Stephan Grabbe and Tobias Bopp).

Dendritic cells: master controls of adaptive immunity

Dendritic cells (DCs) play a central role in maintaining self-tolerance by presenting self-antigens and harmless environmental antigens (peptides) in the absence of stimulatory signals to T cells. T cells that bind to these antigens are inactivated or reprogrammed to so-called (immuno)regulatory T cells (Treg). In addition, DCs that phagocytose a pathogen or pathogen-infected cell play a role in activating antigen-specific effector T cells. Activated cytotoxic T cells (CTL) can directly kill infected cells and tumour cells, while other activated T cells exert helper functions (Th cells) and promote CTL activation.

Due to their versatile role, DCs are interesting targets for immunotherapeutic strategies to treat autoimmune and allergic diseases, or to mount profound and sustained anti-tumour responses. We work to test multi-functionalised nano-vaccines for their ability to activate DCs and stimulate DC-mediated T cells, as well as testing candidate vaccines in tumour mouse models. In addition, we study where immunotherapeutic nanoparticles travel in the body after intravenous injection, and elucidate the mechanisms by which they are retained in the liver.

β2 integrins: leukocyte adhesion molecules with multiple immune functions

β2 integrin receptors are expressed specifically by leukocytes. They

have many functions in the immune system; some bind ICAMs, providing a scaffold for interactions between immune cells, while others enable leukocytes to roll along the endothelium in search of inflammation sites or function as phagocytic receptors for complement-opsonised pathogens and immune complexes.

We study the roles that β2 integrins play in maintaining tolerance and how their dysregulation contributes to autoimmune disease, with the goal of discovering therapeutic treatments. For this purpose, we generated a mouse strain with a floxed CD18 gene locus, which enables us to study the distinct roles of β2 integrins in DC, Treg and neutrophil cells. Interestingly, mice with a selective defect of β2 integrins in Treg develop a spontaneous Th2 phenotype that fulfils all the criteria of human atopy. Using single-cell gene expression analyses as well as functional *in vitro* and *in vivo* assays, we are currently aiming at obtaining a better understanding of how β2 integrins control T helper cell differentiation.

Tumour immunotherapy

Tumours can be recognised and destroyed by the immune system, but often manage to escape destruction. Using murine melanoma models and patient-derived tumour samples, we work to understand key elements of the interaction between the immune system and tumours, and develop anti-cancer immunotherapeutic strategies using nanoparticle-based approaches or by modulating the tumour microenvironment with β2 integrins.

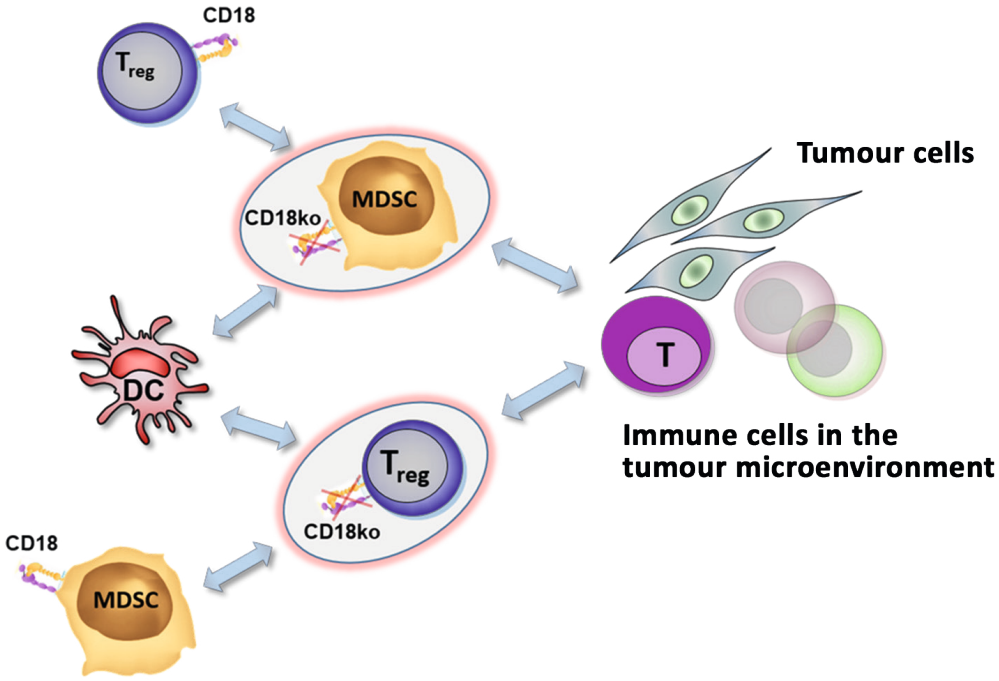

Figure 1

Relevance of β2 integrins for regulatory cell functions in tumours.

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Kappel C, Seidl C, Medina-Montano C, Schinnerer M, Alberg I, Leps C, Sohl J, Hartmann AK, Fichter M, Kuske M, Schunke J, Kuhn G, Tubbe I, Paßlick D, Hobernik D, Bent R, Haas K, Montermann E, Walzer K, Diken M, Schmidt M, Zentel R, Nuhn L, Schild H, Tenzer S, Mailänder V, Barz M, Bros M# and Grabbe S# (2021) Density of conjugated antibody determines the extent of Fc receptor dependent capture of nanoparticles by liver sinusoidal endothelial cells. *ACS Nano*, 15:15191-15209

#indicates joint correspondence

Susann **Schweiger**

> We work to translate discoveries from basic research into treatments for neurodegenerative & neurodevelopmental diseases.

POSITIONS HELD

Since 2022	Adjunct Clinician, Institute of Molecular Biology (IMB), Mainz
Since 2020	Group Leader, Leibniz Institute for Resilience Research (LIR), Mainz
Since 2012	Director, Institute of Human Genetics, University Medical Center (UMC), Mainz
2007 – 2012	Professor of Molecular Medicine, Dundee Medical School
2010 – 2012	Vice Chair, Wellcome Trust Center for Molecular Medicine, Dundee
2005 – 2010	Lichtenberg Professor, Charité-Berlin
2001 – 2005	Group Leader, Max Planck Institute for Molecular Medicine, Berlin

EDUCATION

2006	Board Certificate in Human Genetics, Charité-Berlin
1993	MD in Biochemistry, University of Freiburg
1993	Medical School, University of Freiburg
1989	Medical School, University of Innsbruck

DISCOVER MORE

RESEARCH HIGHLIGHTS

In our genetics clinic, we see a large variety of patients with rare diseases, with a particular focus on neurodevelopmental and neurodegenerative disorders. We study mutations in our patients in combination with their phenotypes in order to understand gene function in humans. We also use reprogramming of patients' cells and differentiate induced pluripotent stem cells into neural precursor cells, neurons and cerebral organoids to study gene function and the mechanisms of disease. We put a particular emphasis on understanding the molecular mechanisms that underlie variability in clinical phenotypes. Mouse models are used for analysis on the organismal level. Finally, we use our patient cohorts with rare diseases and interesting gene defects to complete our methodological repertoire. With all these efforts, we aim to develop experimental therapies for patients with rare disorders.

Early processes in Huntington's Disease

Huntington's Disease (HD) is a late-onset and devastating neurodegenerative disorder that is very hard to detect in the early stages. However, once the disease has reached the symptomatic phase, neurodegeneration is already far advanced and therapy is likely to be too late. Using mouse models of HD, we have found aberrations in the cortical network at a very early stage before disease onset; these were associated with subtle behavioural abnormalities. We found that the synthesis of the disease-causing protein in HD is driven by a protein complex that contains the mTOR kinase (mammalian target of rapamycin). Metformin inhibits the formation of this complex and, as we can show, substantially reduces the production of disease-causing protein in an animal model of HD. Currently, we are following the hypothesis that huntingtin RNA and proteins assemble in a condensate with the mTOR kinase and protein phosphatase 2A through phase separation, and that metformin and other small compounds might interfere with this. Furthermore, we are investigating whether early treatment with metformin can improve later disease progression in the mouse and have put together a clinical trial for patients before disease onset.

Patients with telomeropathies

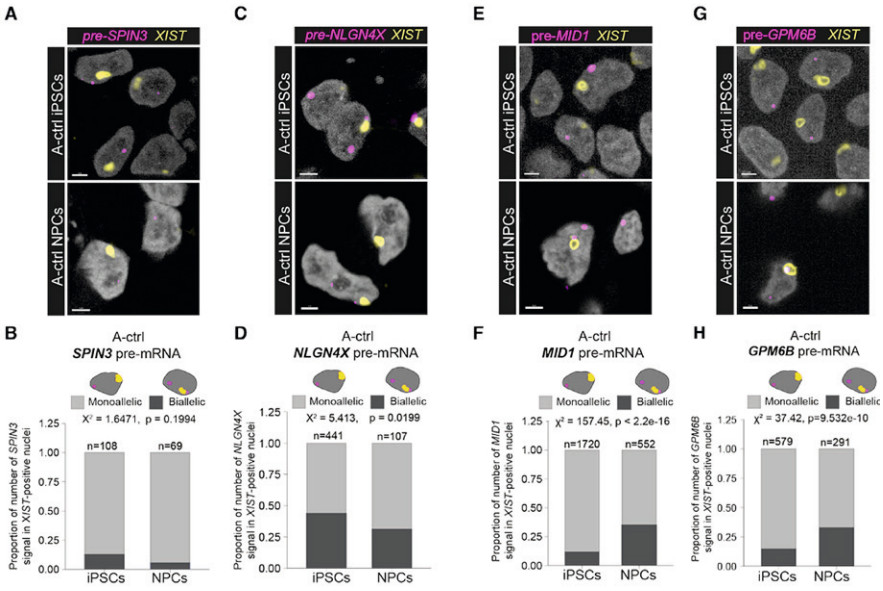
In our rare disease clinic, we have identified a three-generation family with dyskeratosis congenita. Patients are characterised by early greying of hair, hyperpigmentation of the neck, pulmonary fibrosis and bone marrow failure, among other things. We have found a target mutation in the *TERC* RNA in three members of the family. We have further searched for reasons for a significant anticipation of disease symptoms in the third generation and identified an *RTEL1* mutation on top of the *TERC* mutation coming from the paternal side of the family. Telomeres of *TERC* mutation carriers were short, while telomeres of *TERC* and *RTEL1* mutation carriers, as well as those with only *RTEL1* mutations, were very short. Together with the group of Peter Baumann (IMB/JGU), we have established Nanopore technology to analyse the telomeres of the affected patients base by base. Furthermore, we are establishing telomerase-negative fibroblasts and telomerase-positive induced pluripotent stem cells and lymphoblastoid cells to observe how telomeres behave in the proliferating cells of affected patients.

We are using the fruitful collaboration with the Baumann lab and with the clinical departments of Pneumonology (Michael Kreuter) and Haematology to establish a core unit for telomeropathies in Mainz that ranges from basic telomere research to routine diagnostics and therapy development.

Dynamic X-chromosomal reactivation enhances female brain resilience

Sexual dimorphism is well-documented in neurodevelopmental disorders, but the underlying molecular mechanisms are not well understood. One of the most important differences between male and female mammals is the sex chromosomes. In order to allow dosage compensation between the sexes, large parts of one X chromosome are randomly inactivated in females. Using induced pluripotent stem cells, neural precursor cells, neurons and brain organoids as models, we have found that the expression of X-chromosomal genes can be dynamically reactivated from the inactive X-chromosome during neurodevelopment, thereby allowing facultative escape of selected genes. This substantially influences the phenotype and development of X-linked neurodevelopmental diseases in females, adding an extra layer of resilience in the female brain.

In collaboration with the ReALity community and with Felicia Basilicata (UMC) and Peter Baumann (IMB/JGU) and collaboration partners in Münster, we will follow the hypothesis that not only differentiation but also neuronal activation induces reactivation of gene expression from the inactive X chromosome. This might lead to a dimorphic gene expression signature that already arises in the perceiving neuron and could be the root of sex-dependent perception. We also plan to study X chromosomal gene reactivation in the developing immune system and during ageing, and will work together with Stamatis Papathanasiou (IMB) to understand the molecular mechanisms underlying X chromosomal reactivation.



▲ **Figure 1**

Reactivation of gene expression from the inactive X chromosome, as shown by pre-mRNA FISH on the single-cell level. A, B) *SPIN3* stays monoallelic during differentiation, C, D) *NLGN4X* escapes inactivation and is biallelically expressed throughout differentiation. E-H) *MID1* and *GPM6B* change from monoallelic to biallelic expression during neuronal differentiation.

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Rücklé C*, Körtel N*, Basilicata MF, Busch A, Zhou Y, Hoch-Kraft P, Tretow K, Kielisch F, Bertin M, Pradhan M, Musheev M, Schweiger S, Niehrs C, Rausch O, Zarnack K, Keller Valsecchi CI and König J (2023) RNA stability controlled by m^{6}A methylation contributes to X-to-autosome dosage compensation in mammals. *Nat Struct Mol Biol*, 30:1207-1215

Cooper A, Butto T*, Hammer N*, Jagannath S, Fend-Guella DL, Akhtar J, Radyushkin K, Lesage F, Winter J, Strand S, Roeper J, Zechner U# and Schweiger S# (2020) Inhibition of histone deacetylation rescues phenotype in a mouse model of Birk-Barel intellectual disability syndrome. *Nat Commun*, 11:480

*indicates joint contribution, #indicates joint correspondence

Oliver **Tüscher**

> We work to discover the molecular mechanisms of resilience in ageing.

POSITIONS HELD

Since 2024	Chair of Psychiatry, Psychotherapy & Psychosomatics, University Medicine Halle (Saale)
Since 2022	Adjunct Clinician, Institute for Molecular Biology (IMB), Mainz
Since 2020	Founding Member, Research Group Leader & Head of the Clinical Investigation Center (CIC), Leibniz Institute for Resilience Research (LIR), Mainz
Since 2016	Professor of Mental Health & Cognitive Resilience in Old Age, University Medical Center (UMC) & German Resilience Center (DRZ), Mainz
Since 2015	Vice-chair of Psychiatry, UMC, Mainz
Since 2013	Attending in Psychiatry & Psychotherapy, UMC, Mainz
2010 – 2013	Residency in Psychiatry & Psychotherapy, UMC, Mainz
2009 – 2010	Residency in Psychiatry & Psychotherapy, University of Freiburg
2006 – 2010	Head of the Emotion Regulation & Impulse Control Imaging Group (ERIC), Freiburg Brain Imaging, University of Freiburg
2006 – 2009	Residency in Neurology, University of Freiburg
2003 – 2006	Postdoc, Weill Medical College Cornell University, New York
2001 – 2003	Residency in Neurology, University Medical Center Hamburg-Eppendorf, University of Hamburg

EDUCATION

2013	Board Certification for Psychiatry and Psychotherapy
2010	Board Certification for Neurology
2011	Habilitation in Neurology, University of Freiburg
2002	MD/PhD in Neurobiology, University of Heidelberg
2000	Medical School, University of Heidelberg
1995	Medical School, University of Bochum

DISCOVER MORE

RESEARCH HIGHLIGHTS

Our research focus is on resilience mechanisms in healthy ageing, neurodegeneration and neuropsychiatry at the Department of Psychiatry and Psychotherapy. The group is co-led by Kristina Endres, Katharina Geschke/Isabel Heinrich and myself. We use a broad spectrum of methods ranging from preclinical lab work to clinical studies to investigate the mechanisms of healthy ageing and resilient ageing in particular. Based on our findings, we aim to develop preventive and disease-modifying therapeutic interventions. Our interdisciplinary research group includes biologists, chemists, computer scientists, psychologists and physicians, enabling us to implement findings from research on molecular mechanisms into clinical use. The results of our investigations are evaluated using a translational cycle, with the ultimate goal of fostering an ageing process that is as cognitively healthy and free of ailments as possible.

We work in close cooperation with the Centre for Healthy Ageing (CHA) to identify and investigate biomarkers and mechanisms of (resilient) healthy ageing in neuronal tissues. Intervention strategies are tested on animal models ranging from *C. elegans* to mice. Using neuroimaging techniques, we translate this research to the human brain and study neural network mechanisms of resilient ageing – a conceptual framework we recently developed to explicitly understand and target those biological mechanisms that protect the brain and body against functional loss caused by ageing and ageing-related diseases. Studies in our lab include the following areas:

Resilient ageing: ReALizing healthy body & brain ageing (ReALity HBBA)

We are investigating the mechanism(s) conveying resilience to body and brain ageing by comprehensively assessing the (epi)genomic, proteomic, cellular-immunologic and cardiovascular phenotypes of participants in the AgeGain study (with the Bopp Lab, FZI/UMC and the Wild Lab, CTH/UMC & IMB). On the methylome level, we have been able to show that resilient ageing is associated with having a significantly younger biological age (PhenoAge epigenetic

clock) compared to "normal agers" (in collaboration with the Wild/Niehrs ReALity Project EpiHF). Intriguingly, PhenoAge correlates with the volume and the connectivity of memory-related brain structures (see Figure 1). We will further uncover the genetic and cellular senescence mechanisms related to this by comparing resilient and non-resilient participants (in collaboration with the Baumann Lab, JGU/IMB) (Fischer *et al.*, 2024, *iScience*).

Gut-brain axis in ageing

Recent studies suggest that certain bacterial commensals may cause accelerated or diseased ageing. We study the gastrointestinal system in mouse models of Alzheimer's disease and accelerated ageing (together with the Baumann (IMB/JGU) and Schick (IMB) labs through the CHA and Science of Healthy Ageing Research Programme) to identify pathways that can serve as new therapeutic treatment options to ameliorate cognitive decline in ageing (Nguyen *et al.*, 2023, *Int J Mol Sci*).

Signatures of vulnerability in the ageing brain

Certain brain regions maintain function throughout ageing and even diseased ageing, while others are highly vulnerable. Together with the Dormann (JGU/IMB), Gerber (UMC) and Bopp (UMC) labs, we analyse how different brain areas and cellular subpopulations in the brain are affected by normal and accelerated ageing. With the Krämer-Albers lab (JGU), we also analyse neuronal extracellular vesicles in humans to unravel novel biomarkers of cognitively healthy ageing (Brahmer *et al.*, 2023, *Cell Commun Signal*).

Anti-brain ageing therapeutics

We are evaluating the use of sarcopenia (the progressive loss of strength and functionality of skeletal muscles) as an external measure of healthy ageing in rodent models and humans, and are using it to assess the efficacy of therapeutic interventions for Alzheimer's disease and preventing cognitive decline in normal and accelerated ageing. We have just shown that 5xFAD mice (which are used as models of neurodegeneration) had significantly lower quantities of *Bacteroides* spp. in their gut microbiota when only considering frailty, and lower levels of *Bacteroidetes* when considering both frailty and chronological age compared to their wild-type littermates. Thus, the quality of ageing—as assessed by frailty measures—should be taken into account to unravel potential changes in the gut microbial community in Alzheimer's disease (Kapphan *et al.*, 2023, *Microorganisms*).

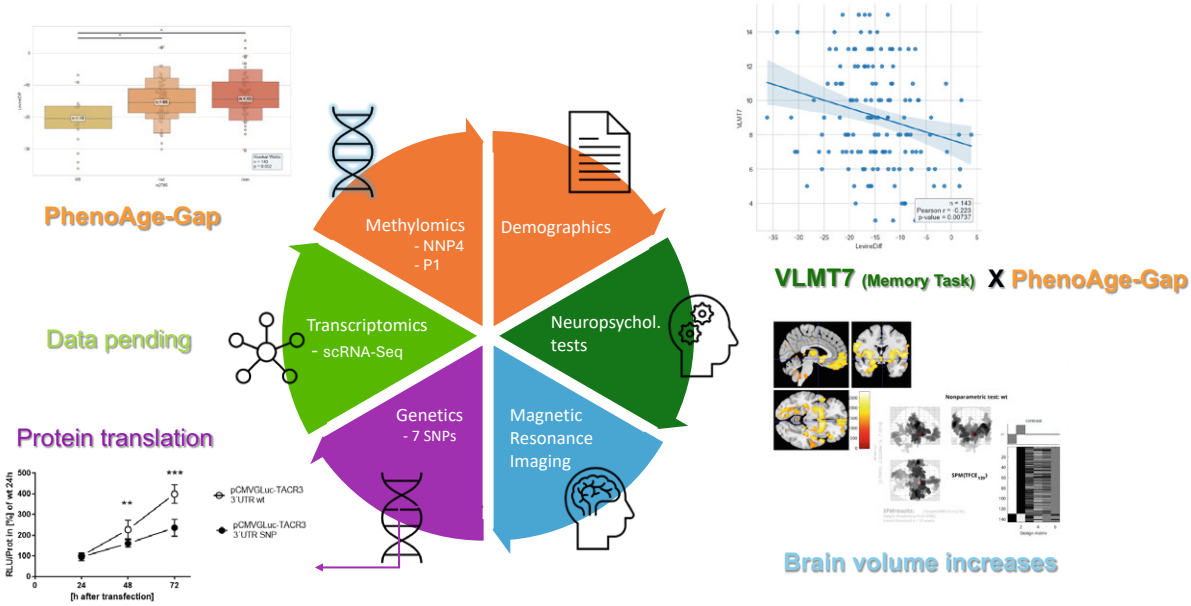


Figure 1

Summary of our multimodal translational approach to identify molecular mechanisms of resilient ageing, exemplified here with the neurokinin-3 receptor *TACR3* gene variant (rs2765).

SELECTED PUBLICATIONS

Tüscher O*, Muthuraman M*, Horstmann JP*, Horta G, Radyushkin K, Baumgart J, Sigurdsson T, Endle H, Ji H, Kuhnhäuser P, Götz J, Kepser LJ, Lotze M, Grabe HJ, Völzke H, Leehr EJ, Meinert S, Opel N, Richers S, Stroh A, Daun S, Tittgemeyer M, Uphaus T, Steffen F, Zipp F, Groß J, Groppa S, Dannlowski U, Nitsch R and Vogt J (2024) Altered cortical synaptic lipid signaling leads to intermediate phenotypes of mental disorders. *Mol Psychiatry*, 29:3537-3552

Stroh A, Schweiger S, Ramirez JM and Tüscher O (2024) The selfish network: how the brain preserves behavioral function through shifts in neuronal network state. *Trends Neurosci*, 47:246-258

Fischer FU, Gerber S and Tüscher O; Alzheimer's Disease Neuroimaging Initiative (2024) Mathematical model of the Alzheimer's disease biomarker cascade demonstrates statistical pitfall in identifying surrogates of cognitive reserve. *iScience*, 27:111188

*indicates joint contribution

Philipp **Wild**

> We use systems medicine to understand the pathomechanisms of age-related disease.

POSITIONS HELD

Since 2022	Adjunct Clinician, Institute of Molecular Biology (IMB), Mainz
Since 2020	Rhine-Main Deputy Site Speaker, German Center for Cardiovascular Research (DZHK)
Since 2015	Head of Liquid Biobank, University Medical Center (UMC), Mainz
Since 2015	Speaker, Research Center for Translational Vascular Biology (CTVB), UMC, Mainz
Since 2013	Head of Preventive Cardiology and Preventive Medicine, Center for Cardiology, UMC, Mainz
Since 2012	Professor of Clinical Epidemiology, Center for Thrombosis & Hemostasis (CTH), UMC, Mainz
Since 2012	Head of Clinical Epidemiology & Systems Medicine, Center for Thrombosis & Hemostasis (CTH), UMC, Mainz
Since 2011	Coordinating Principal Investigator & Steering Committee Member of the Gutenberg Health Study (GHS), UMC, Mainz
2010 – 2012	Senior Physician, UMC, Mainz

EDUCATION

2022	Board certification in Cardiology
2012	MSc in Epidemiology, IMBEI, UMC, Mainz
2009	Board certification in Internal Medicine
2004	MD, Philipps University Marburg
2002	Medical School, Leipzig University and Philipps University Marburg

DISCOVER MORE

RESEARCH HIGHLIGHTS

Systems medicine – a holistic approach to promoting healthy ageing

The Systems Medicine Group has comprehensive experience in molecular epidemiology and systems medicine research. We focus on investigating complex common diseases, which are strongly driven by the ageing process. Our research themes range from cardiovascular diseases to cardiometabolic conditions, as well as infectious diseases (e.g. SARS-CoV-2) and cancers. The study of how the ageing process induces pathological changes is a key priority for our group.

Developing tailor-made therapeutic treatments for disease

Using artificial intelligence (AI) methods and state-of-the-art high-throughput omics profiling, we holistically integrate multi-omics data with environmental exposures, (sub)clinical parameters and advanced imaging data to discover new biomarkers and biosignatures, detect diseases earlier and predict their further progression. This is the basis for the development of tailor-made therapies, diagnostics, prognostics and therapy monitoring tools to determine a patient's response to therapy.

Exemplary highlights

The Federal Ministry of Education and Research (BMBF)-funded cluster of excellence *curATime* (funding for the first 3 of 9 years: €15 million), in which our group has multiple projects, opened several promising avenues for joint academic-industrial exploration of new therapeutic targets in cardiovascular medicine. Through the unique combination of extensive human and murine multi-omics and other multimodal data and advanced AI methods, the *curATime* cluster is on track to produce high-ranking academic output, while continuing to honour its focus of contributing to precision cardiovascular medicine through intensive academic-industrial collaboration.

As part of the BMBF-funded project MSCoreSys (Research cores for mass spectrometry in systems medicine), the multidisciplinary Mainz research core DIASyM, which I am co-heading, is developing and optimising innovative methods and workflows to improve our

understanding of the complex pathomechanisms underlying the development and progression of heart failure.

Last year, the group received funding from the Carl-Zeiss Foundation for *Multi-dimensionAI*, a multi-site initiative to advance the diagnosis and treatment of heart failure with preserved ejection fraction (HFpEF) through cutting-edge AI. The project will utilise novel AI algorithms to analyse diverse patient data across multiple scales, from molecular-level omics data to broader medical imaging, enabling a more comprehensive understanding of HFpEF.

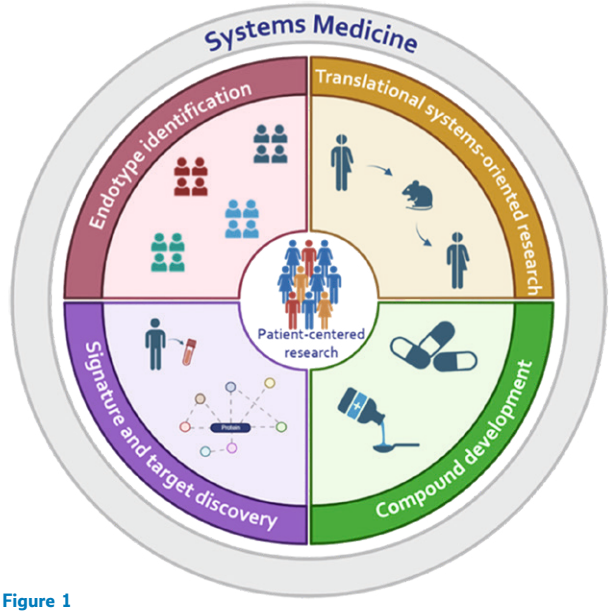
We have also expanded our scope to lung cancer, taking part in the LUCAS (Lung cancer screening) consortium funded by the BMBF. This project investigates DNA methylation and proteomic profiles of individuals with diagnosed lung cancer in large population-based cohorts in collaboration with the University Cancer Center Mainz (UCT) (Thomas Kindler), DKFZ Heidelberg (Hermann Brenner) and UMIT Tirol (Uwe Siebert). The goal is to develop a non-invasive method of early patient identification that can contribute to the early triage of individuals at risk of lung cancer, so as to ultimately diagnose lung cancer at an earlier and more treatable stage.

Two new projects were launched in the BMBF-funded research network EPIC-AI, where we are investigating the complex and heterogeneous pathomechanisms of post-COVID syndrome. Using AI techniques, endotypes will be identified based on highly granular (sub-)clinical and molecular data. The team will evaluate (off-label) therapies used to treat post-COVID patients (*TheraSurv Post-COVID*) in a project funded by the Ministry of Science and Health of Rhineland-Palatinate. Using an app-based surveillance system, physicians treating post-COVID patients will enter medical treatment data into a digital registry, and the health status of the patients will be monitored weekly via smartphone-based assessments.

In the context of IMI SOPHIA, our group contributed to developing a breakthrough clinical risk prediction algorithm that categorises obesity into five distinct diagnostic profiles, each with different health consequences and treatment needs (Coral *et al.*, 2024, *Nat Med*). About 20% of the population had health markers that did not match what was expected for their body weight. For example, 8% of women had elevated blood pressure, while their cholesterol levels and body fat distribution were healthier than expected, a pattern not observed in men.

The Systems Medicine group has also significantly expanded its multi-omics resources: following the successful establishment and certification of the high-plex proteomics platform Olink Explore, based on affinity-NGS and the Proximity Extension Assay (PEA) technology, this platform was expanded to the new Explore HT system. Explore HT enables the simultaneous quantification of 5,416 proteins, making it one of the two most advanced high-plex proteomics platforms. Our laboratory was one of the first in the world to be certified for the Explore platform. To date, almost 4,000 samples from large-scale internal human studies and external cooperation partners have been analysed. The resulting comprehensive system-wide protein profiles in several biobanks have enabled unprecedented in-depth proteomic phenotyping and the identification of disease-related pathomechanisms.

In addition, the group has further expanded its clinical epigenetics resources by obtaining more DNA methylation measurements (Illumina MethylationEPIC 850k array). With a combined sample size of more than 5,000 individuals, this dataset is one of the five largest cohorts with epigenetic data on cardiovascular disease. The project builds on the existing EpiHF project, a collaboration of the ReALity/Science of Healthy Ageing Research Programme network.



▲ **Figure 1**

Areas of clinical medicine studied by the Systems Medicine Group.

SELECTED PUBLICATIONS

Müller FS, Aherrahrou Z, Grasshoff H, Heidorn MW, Humrich JY, Johanson L, Aherrahrou R, Reinberger T, Schulz A, Ten Cate V, Robles AP, Koeck T, Rapp S, Lange T, Brachaczek L, Luebber F, Erdmann J, Heidecke H, Schulze-Forster K, Dechend R, Lackner KJ, Pfeiffer N, Ghaemi Kerahrodi J, Tüscher O, Schwarting A, Strauch K, Münzel T, Prochaska JH, Riemekasten G, and Wild PS (2023) Autoantibodies against the chemokine receptor 3 predict cardiovascular risk. *Eur Heart J*, 44:4935–4949

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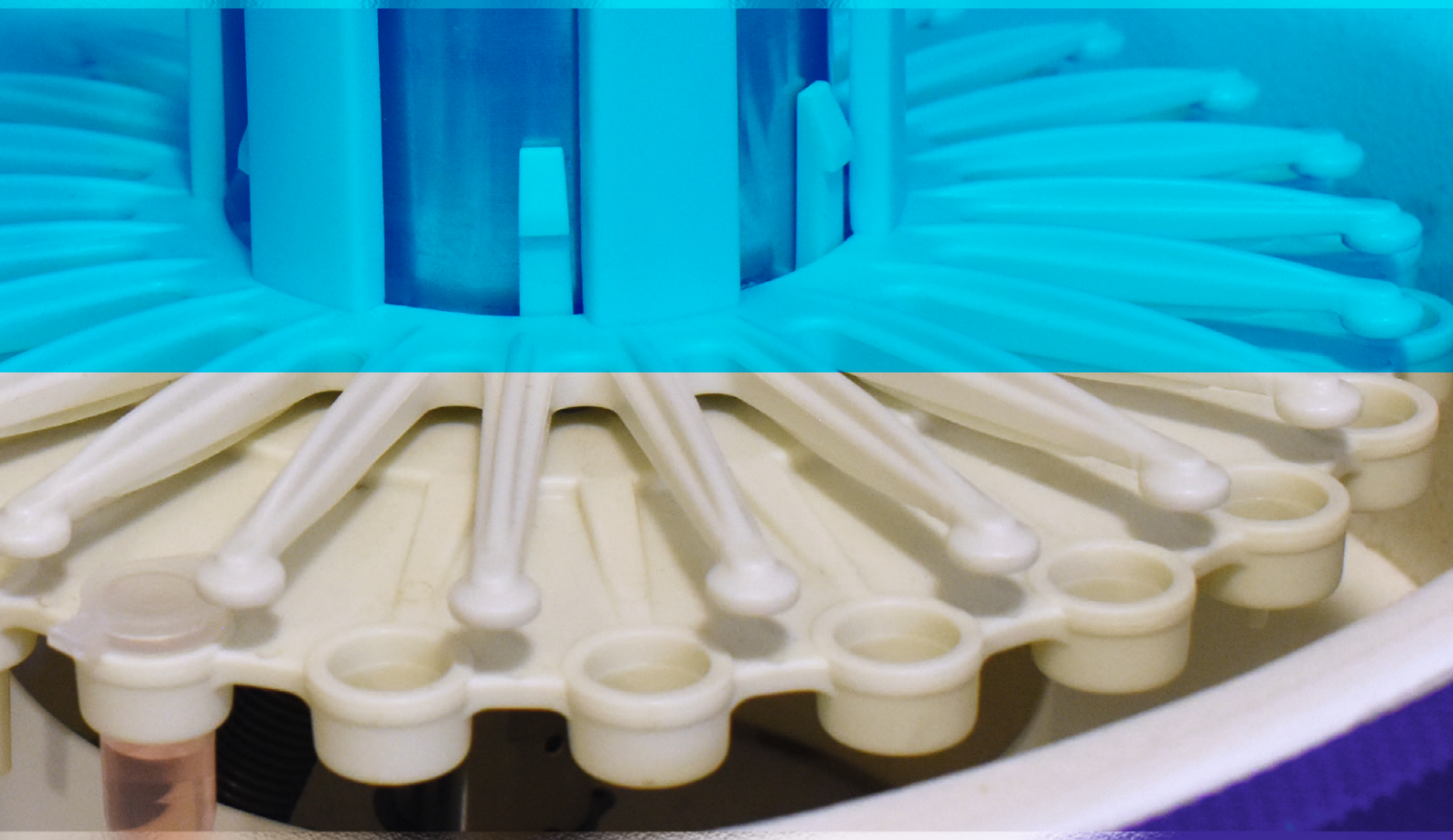
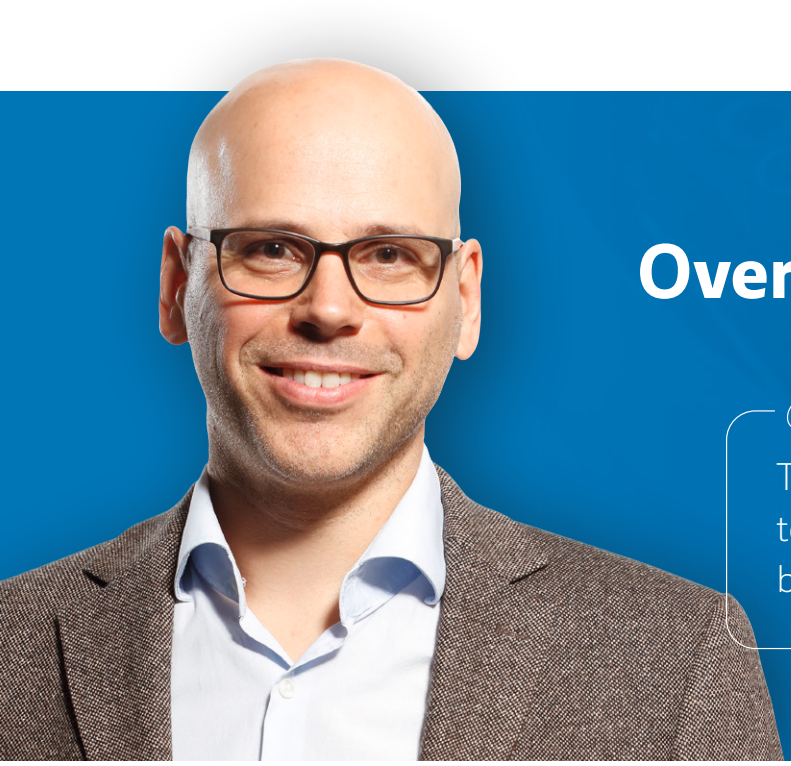
Ten Cate V, Prochaska JH, Schulz A, Koeck T, Pallares Robles A, Lenz M, Eggebrecht L, Rapp S, Panova-Noeva M, Ghofrani HA, Meyer FJ, Espinola-Klein C, Lackner KJ, Michal M, Schuster AK, Strauch K, Zink AM, Laux V, Heitmeier S, Konstantinides SV, Münzel T, Andrade-Navarro MA, Leineweber K and Wild PS (2021) Protein expression profiling suggests relevance of noncanonical pathways in isolated pulmonary embolism. *Blood*, 137:2681–2693

CORE FACILITIES





Overview

> The Core Facilities provide access to key technologies, as well as support & training by experts.

The Bioinformatics, Genomics and Proteomics Core Facilities (CFs) provide a "full service", covering experimental design and quality control for the generation, analysis and presentation of data. The Flow Cytometry and Microscopy/Histology CFs provide an "assisted service", where researchers work independently on CF equipment after training. CF staff are available for consultation and troubleshooting for all users. Furthermore, we offer collaborations for customised or specialised services. IMB researchers can access all CFs, while external users in Mainz can access the Flow Cytometry, Genomics, Microscopy/Histology and Proteomics CFs. In addition, many CFs are involved in supporting IMB's collaborative research initiatives.

We adjust CF services based on user demand. Each facility has a user committee to provide feedback on the equipment and user experience. This also helps determine the implementation of new CF services.

Innovation is a pivotal aspect of the facilities. One example is the recent formation of the "Competence Hub for Single-Cell Genomics" and the "Competence Hub for Spatial Transcriptomics". These hubs combine the expertise and service of two core facilities to develop new methods that go beyond the standard services of any individual facility. In 2025, we established a new "Competence Hub for Biomedical AI Applications", where experts from many CFs as well as other areas of IMB work together to implement AI tools.

We offer lectures and practical courses on new techniques and instruments, experimental design, statistics and data acquisition, processing and analysis to allow researchers to keep up-to-date with current and emerging technologies. Lectures are open to everyone, including those outside IMB.

The CFs also run "Core Support Units" (CSU). The Core Equipment unit maintains a broad range of standard lab equipment and offers training as well as troubleshooting for them. The Media Lab unit supplies internal researchers with a variety of buffers, solutions and agar plates. Additional CSUs include the radionuclide lab, the S2 lab, in-house animal facilities for mice, zebrafish and *Xenopus*, and IT support.

Andreas Vonderheit
Director of Core Facilities and Technology

Bioinformatics

> The Bioinformatics Core Facility supports the analysis, interpretation & publication of next-generation sequencing & other complex datasets.

SERVICES OFFERED

The Bioinformatics Core Facility assists researchers with computing infrastructure, software training, experimental design, biostatistics and data analysis. Our staff offer different levels of support depending on project needs:

- Consulting on biostatistics and the experimental design of genomics projects
- Data quality assessment, processing, analysis, visualisation and interpretation
- Implementation of next-generation sequencing (NGS) analysis pipelines and customisation for individual projects
- Development of novel tools and custom methods for specific analysis tasks
- Data mining and integrative analysis of internal and published datasets
- Assistance with preparing manuscripts, presentations and grant proposals
- Testing, implementation and customisation of software tools and services
- Training courses in bioinformatics, high-performance computing, and biostatistics

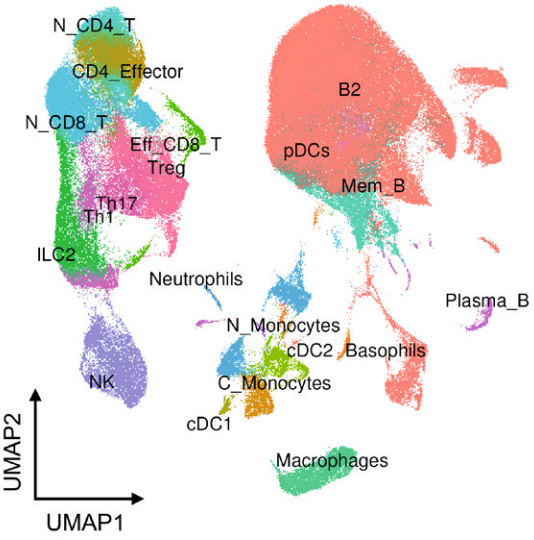
To facilitate reproducible and scalable data analysis, we maintain software repositories with various tools and pipelines used by both core facility staff and data analysts in the research groups. Our facility has been containerising the software tools and implementing state-of-the-art development practices through continuous integration and deployment with GitLab. Beyond individual project support, we have been involved in several institutional and interdisciplinary initiatives, including the Collaborative Research Centre on "Regulation of DNA Repair and Genome Stability" (CRC 1361) and the "Science of Healthy Ageing Research Programme" (SHARP) in Mainz.

In collaboration with the Genomics, Flow Cytometry, and Microscopy Core Facilities, we have established two Competence Hubs for Single-Cell Genomics and for Spatial Transcriptomics, offering analytical expertise and pipeline development for these rapidly evolving technologies. Our facility also recently contributed to the formation of a Competence Hub for Biomedical AI Applications, which aims to explore and implement artificial intelligence approaches in life science research. With our integrated expertise, modern infrastructure and collaborative spirit, the Bioinformatics Core Facility plays a key role in driving computational and analytical innovation at IMB.

CORE FACILITY MEMBERS

Head Emil Karaulanov
Bioinformaticians Anke Busch, Patrick Hüther, Sivarajan Karunanithi, Nastasja Kreim, Michal Levin, Giuseppe Petrosino, Frank Rühle
Biostatistician Fridolin Kielisch

DISCOVER MORE



▲ **Figure 1**
UMAP representation of over 250,000 immune cells from a mouse spleen single-cell RNA-Seq data set. Cell clusters were annotated with the ScType tool (PMC8913782) using custom marker genes.

Flow Cytometry

> The Flow Cytometry Core Facility offers high-throughput measurements, analysis & separation of biological units.

CORE FACILITY MEMBERS

Head Stefanie Möckel
Staff Scientist Stephanie Nick

DISCOVER MORE

SERVICES OFFERED

We offer a full service for sorting and an assisted service with training for the analysers. Additionally, staff members are available for collaborations to analyse flow cytometry data and prepare samples. During the past year, the facility has performed multicolour measurements, sorted isolated neuronal nuclei and performed classical enrichments for subsequent cell culture, qPCR analysis, mass spectrometry and microscopy. We work with many different materials, including nuclei, stem cells, yeast, *C. elegans* and autophagosomes, as well as various cultured cell lines and primary cells from humans, mice, zebrafish and *Drosophila*. To educate and train users, the facility offers three lectures, an annual practical course for basic flow cytometry analysis and an advanced practical course for cell sorting.

In 2025, we co-organised and attended the 2nd German Flow Core Summit in Freiburg, and Stefanie represented IMB's Flow Cytometry Core Facility at CYTO in Denver. Staff also participated in the Bigfoot User Group Meeting in Barcelona, where they were trained on how to sort chromosomes at the Flow Cytometry Unit of the Center for Genomic Regulation. We plan to establish this technique as a new service for IMB users in the near future.

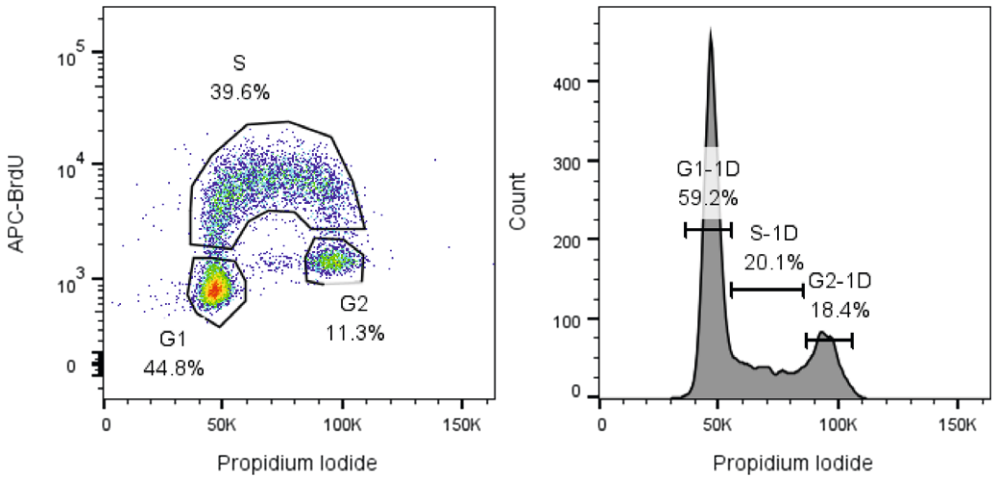


Figure 1

2D cell cycle analysis prevents underestimation of the S-phase population. Cell cycle distribution analysed by 2D (left) and 1D (right) flow cytometry. The 2D plot, incorporating information on DNA content (propidium Iodide) and synthesis (APC-BrdU), accurately resolves S-phase cells (39.6%), while the 1D histogram underestimates this population (20.1%). This highlights the importance of 2D analysis for precise cell cycle quantification.

Genomics

> We provide NGS services using the Illumina NextSeq 2000 & MiniSeq platforms, alongside long-read sequencing from Oxford Nanopore Technologies.

SERVICES OFFERED

The Genomics Core Facility provides a full service for next-generation sequencing (NGS), beginning with the experimental design of the project and continuing all the way to the generation of sequencing data.

We support researchers from IMB, Mainz University, the University Medical Center and other scientists from outside Mainz with comprehensive library preparation workflows for RNA or DNA across a wide range of applications.

All libraries are prepared using validated standard operating procedures. As genomics technologies rapidly evolve, we actively integrate new protocols to stay at the forefront of innovation and meet our researchers' growing and changing needs. In addition, we assist laboratories in the development and optimisation of custom NGS protocols. The facility also accepts and processes self-prepared libraries from IMB researchers.

Figure 1 MiniSeq benchtop sequencer from Illumina.

RNA applications:

- Strand-specific mRNA-Seq with poly-A selection
- Strand-specific total RNA-Seq with rRNA depletion
- Low input RNA-Seq
- QuantSeq 3′ mRNA-Seq
- Small RNA-Seq
- STARR-Seq
- RIP-Seq
- eTAM-Seq
- TT-Seq
- ONT RNA long read sequencing

DNA applications:

- Whole genome sequencing
- ChIP-Seq
- DIP-Seq
- Amplicon-Seq
- ssDNA
- CUT&RUN
- DRIP-Seq, DRIPc-Seq
- STARR-Seq
- dI-Seq
- BrdU-Seq
- 16S sequencing
- ONT DNA long read sequencing
- GLOE-Seq
- BreakTag
- sBLISS
- TrAEL-Seq

CORE FACILITY MEMBERS

Head Maria Mendez-Lago
Staff Scientists Camila Fetiva, Maria Kupper, Giriram Mohana
Technicians Hanna Faber, Ramona Rohde, Joshua Wachlin

DISCOVER MORE

Single-cell sequencing:

- 10x Genomics: Single-cell RNA 3′
- 10x Genomics: Single-cell RNA 3′ fixed RNA profiling
- 10x Genomics: Single-cell multiome (ATAC and gene expression)
- Parse Biosciences single-cell RNA Evercode split-pool combinatorial barcoding
- Scale Biosciences single-cell RNA split-pool combinatorial barcoding

Spatial transcriptomics:

- 10x Genomics: Visium and CytAssist

Microscopy & Histology

> The Microscopy & Histology Core Facility offers a comprehensive array of high-performance microscopes & expert support to ensure top-notch & reliable imaging.

CORE FACILITY MEMBERS

Head Sandra Ritz
Staff Scientists Márton Gelléri, Anusha Bargavi Gopalan, Rossana Piccinno, Petri Turunen

DISCOVER MORE

SERVICES OFFERED

The Microscopy and Histology Core Facility provides state-of-the-art microscopes and histology instruments, as well as expertise and training in sample preparation and data processing. Users can opt for an independent, assisted or full service. In partnership with the Genomics and Bioinformatics Core Facilities, we additionally support the Competence Hub for Spatial Transcriptomics, which provides services for whole-section gene expression analysis in fixed and fresh-frozen tissues.

The facility has 17 instruments, ranging from stereo and wide-field microscopes to confocal, high-content screening and super-resolution microscopes. Eight are equipped for live cell imaging. Image analysis is performed on five high-performance workstations with open-source and licensed software for deconvolution, 3D visualisation and analysis, or fluorescence lifetime analysis. Most of these software tools are capable of image analysis through artificial intelligence, as well as traditional methods.

In 2025, the facility consolidated its use of the Lumicks C-Trap, which integrates confocal microscopy, optical tweezers, and microfluidics for single-molecule biophysics studies. These studies encompass areas such as DNA-protein interactions, protein folding and phase separation. Throughout the year, we also held three practical courses in image processing and analysis, super-resolution microscopy, and quantitative microscopy of (bio)polymers, supported by the CRC 1551.

For histology users, we provide a comprehensive range of techniques, including semi-automated tissue fixation and paraffin embedding. There is also specialised equipment for sectioning, such as a microtome for paraffin-embedded tissues, a cryotome for frozen samples, and a vibratome for gelatin/agarose-embedded or fresh tissues. Furthermore, the facility can assist with optimised protocols for immunodetection and tissue clearing, along with solutions for traditional tissue staining.

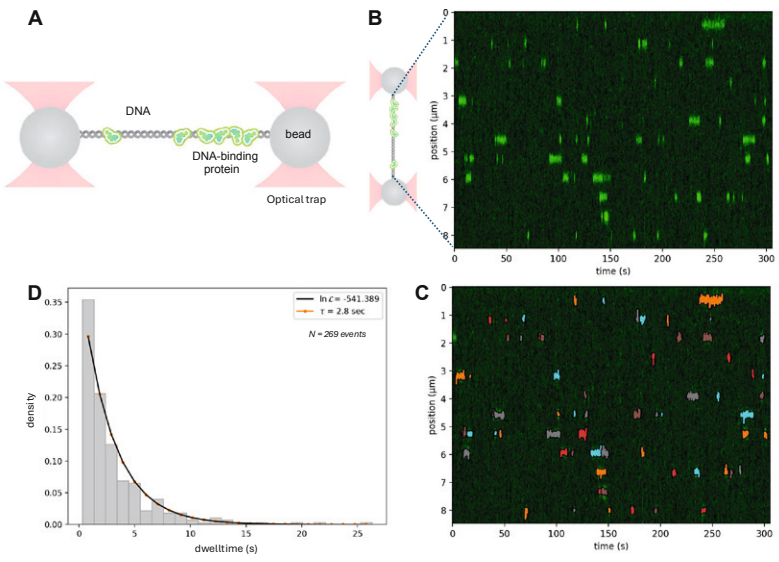


Figure 1

Tracking protein-DNA binding events on the Lumicks C-trap
A) Schematic of a single-molecule binding experiment on the C-trap. B) Example kymograph of Lac-I-ATTO 565 (green) binding to a DNA molecule containing 12x repeats of the LacO binding sequence. C) Tracking of binding events in the kymograph in B. D) Histogram of dwell times from analysing a total of n=269 binding events, fitted to an exponential function, resulting in an estimated off-rate of $1/\tau = 0.36 s^{-1}$ for Lac-I binding to DNA.

Protein Production

> The Protein Production Core Facility assists during all stages of producing & purifying recombinant proteins.

SERVICES OFFERED

The Protein Production Core Facility supports researchers throughout the process of protein production. This includes screening of suitable expression systems and vectors, optimisation of purification steps, upscaling of protein production and purification, as well as functional analysis and (*in vitro*) assay development with the purified products. The facility is equipped with five automated chromatography systems, which enable the latest chromatographic methods for state-of-the-art protein purification strategies.

Another of our key tasks is to generate and perform functional quality control of routine laboratory enzymes and affinity probes for IMB researchers. We currently offer 32 products, matching the most frequently used protein tools at the institute.

The facility consists of a Head and a full-time staff scientist who assist researchers with their project needs and offer services tailored to specific user requests. Since January 2023, the facility has been part of the CRC 1551 on "Polymer Concepts in Cellular Function" and manages a support project alongside the Polymer Analysis Group from the Max Planck Institute for Polymer Research. The main objective is to aid researchers in the production and analysis of intrinsically disordered proteins. To meet these additional demands, the CRC 1551 funds one technical assistant position in the facility.

In 2025, we purified 132 recombinant proteins and antibodies. In most cases, molecular cloning of candidate constructs and expression screenings were also conducted by the facility.

CORE FACILITY MEMBERS

Head Martin Möckel
Staff Scientists Eugenio Ferrario, Sabine Heinen
Technical Assistant Kanish Siddarth Ravi Chandran

DISCOVER MORE

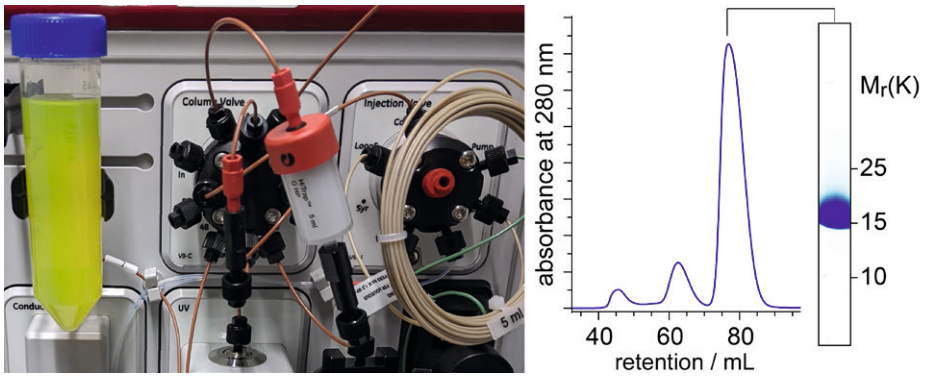


Figure 1

Left: A recombinant protein fused to GFP is purified using a Fast Liquid Chromatography system (FPLC). Right: Elution profile of a recombinant nanobody during the final purification step by gel filtration. The plot shows the absorbance at 280 nm over the column volume (retention). The protein is further visualised by Coomassie-stained SDS-PAGE next to the elution profile.

Proteomics

> The Proteomics Core Facility provides advanced mass spectrometry techniques & flexible, tailored solutions to meet diverse research needs.

CORE FACILITY MEMBERS

Head Jiaxuan Chen
Staff Scientists Christian Blum, Amitkumar Fulzele
Technician Jasmin Cartano
Bioinformatician Mario Dejung

DISCOVER MORE

SERVICES OFFERED

Equipped with multiple high-resolution mass spectrometers and ultra-high-performance liquid chromatography systems, the Proteomics team supports and collaborates with research groups at IMB, Mainz University and beyond. The facility is staffed by wet- and dry-lab scientists with a broad range of research experience and technical expertise.

The facility actively participates in the experimental design of each user project and offers tailored solutions ranging from simple gel band identification to quantitative analysis of complex samples. We support multiple quantitation strategies (label-free, SILAC, di-methyl, TMT), PTM mapping (acetylation, phosphorylation, ubiquitylation) and structural studies using crosslinking mass spectrometry. The Proteomics Core Facility also works closely with users on downstream bioinformatic data analysis to support them in making discoveries from their data. As part of IMB's annual Modern Techniques in Life Sciences lecture series, the facility gives a theoretical lecture on proteomics technologies. Additionally, we offer an annual practical training course on proteomics sample preparation and related bioinformatic data analysis.

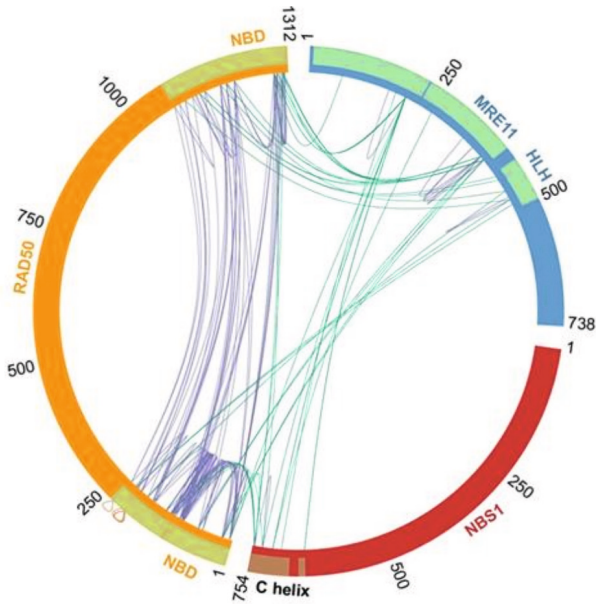


Figure 1 ▶
Circular representation of the molecular structure of the human MRE11-RAD50-NBS1 (MRN) complex, as detected by chemical crosslinking coupled with mass spectrometry (CX-MS). Source: Fan *et al.*, 2025, *Nat Commun*, 16:8320 (Creative Commons Attribution 4.0 International License).

Core Support Units

In addition to the Core Facilities, further infrastructure and support services are provided by smaller Core Support Units (CSUs), which include the following:

→ MEDIA LAB

The Media Lab supports IMB's scientific groups by producing media, buffers and agar plates. It administers three supply centres, S1/S2 waste management and the cleaning and sterilising of glassware. The Media Lab has produced over 60 in-house media and solutions, which are available to researchers 24/7 via a self-service store.

MEMBERS

Head Andrea Haese-Corbit
Assistants Alwina Eirich, Pascal Hagebölling, Annette Holstein, Marion Kay, Monika Kornowska
Student Assistant Katja Göbel

→ CORE EQUIPMENT

The Core Equipment unit maintains a broad range of standard lab equipment and offers comprehensive training as well as troubleshooting for around 50 instruments. It also manages a consumables self-service store that provides researchers with 24/7 access to common lab items and central services for dry ice and liquid nitrogen supplies. In addition, the Core Equipment unit maintains its own workbenches, centrifuges/multifuges and equipment.

MEMBERS

Head Ashley Westerback
Student Assistant Annika Pins

→ IT SUPPORT

The IT Support unit provides comprehensive support for Windows, macOS, hardware, telephones and computer networking. Additionally, two dedicated Linux administrators manage Linux-based servers and oversee the maintenance of IMB's high-performance computing (HPC) cluster, featuring state-of-the-art CPUs and GPUs.

MEMBERS

IT Admins Erias Buxbaum, Pascal Silberhorn
Linux Admins Christian Dietrich, Mike Wendel

→ S2 LAB

The S2 Lab provides bookable workplaces, sterile hoods and incubators in a dedicated S2 area, where IMB groups can conduct their registered S2 work.

→ RADIONUCLIDE LAB

The Radionuclide Lab provides bookable workspaces for working with ^{32}P and ^{35}S.

MEMBERS

Radiation Protection Officers
Laura Frosch, Heike Hänel, Svenja Hellmann

→ ANIMAL FACILITIES

The Animal Facilities support and equip a fish facility with 1,500 tanks, a mouse facility with 330 cages, and a *Xenopus* facility with up to 150 tanks.

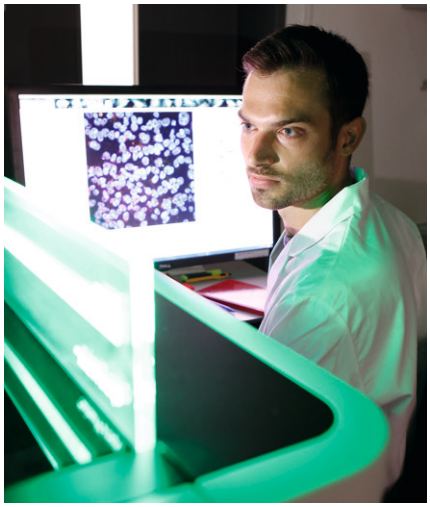
MEMBERS

Animal Caretaker Tamara Dehn

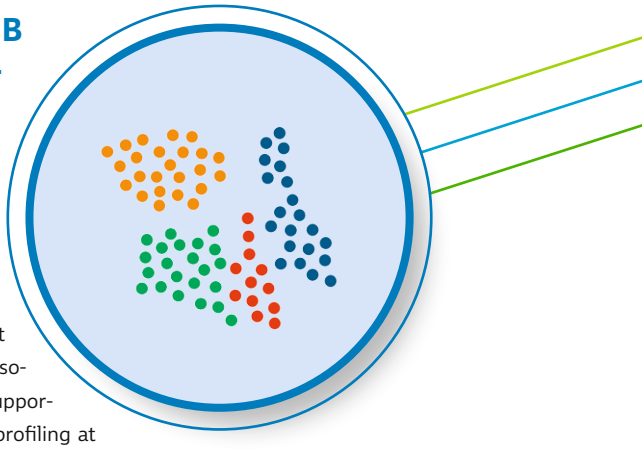
Competence Hubs

To promote interdisciplinary research and the development of new methods that span multiple core facilities, IMB established a series of 'competence hubs' in 2024.

These hubs pool the expertise and infrastructure of several core facilities to provide internal and external researchers with optimised access to cutting-edge technologies and workflows. While cooperation between the individual core facilities has already taken place for several years for individual projects on an ad-hoc basis, the official bundling of these integrated services will result in an expanded range of methods, new synergies and greater innovation potential in the Core Facilities.



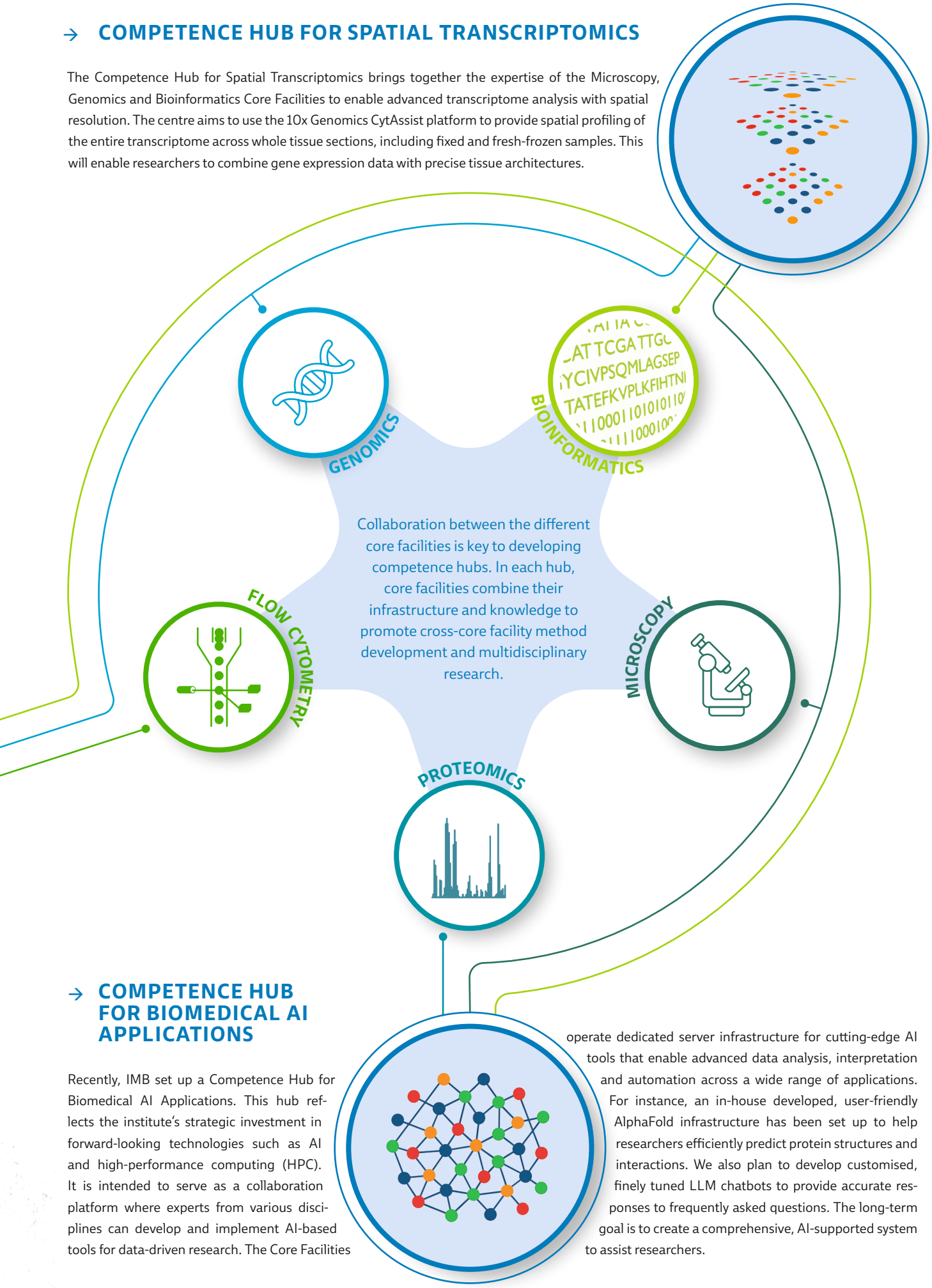
→ COMPETENCE HUB FOR SINGLE-CELL GENOMICS



The Competence Hub for Single-Cell Genomics was established first, building on a collaboration for single-cell sequencing between the Core Facilities for Flow Cytometry, Genomics, and Bioinformatics that has been in place since 2016. It consolidates an integrated approach for supporting high-resolution transcriptome profiling at the single-cell level. The hub combines the expertise and infrastructure of the three core facilities to provide researchers with a seamless, comprehensive service for single-cell studies. The hub aims to support cutting-edge research at single-cell resolution, tailored to a wide range of experimental requirements from cell sorting and sequencing to data analysis.

→ COMPETENCE HUB FOR SPATIAL TRANSCRIPTOMICS

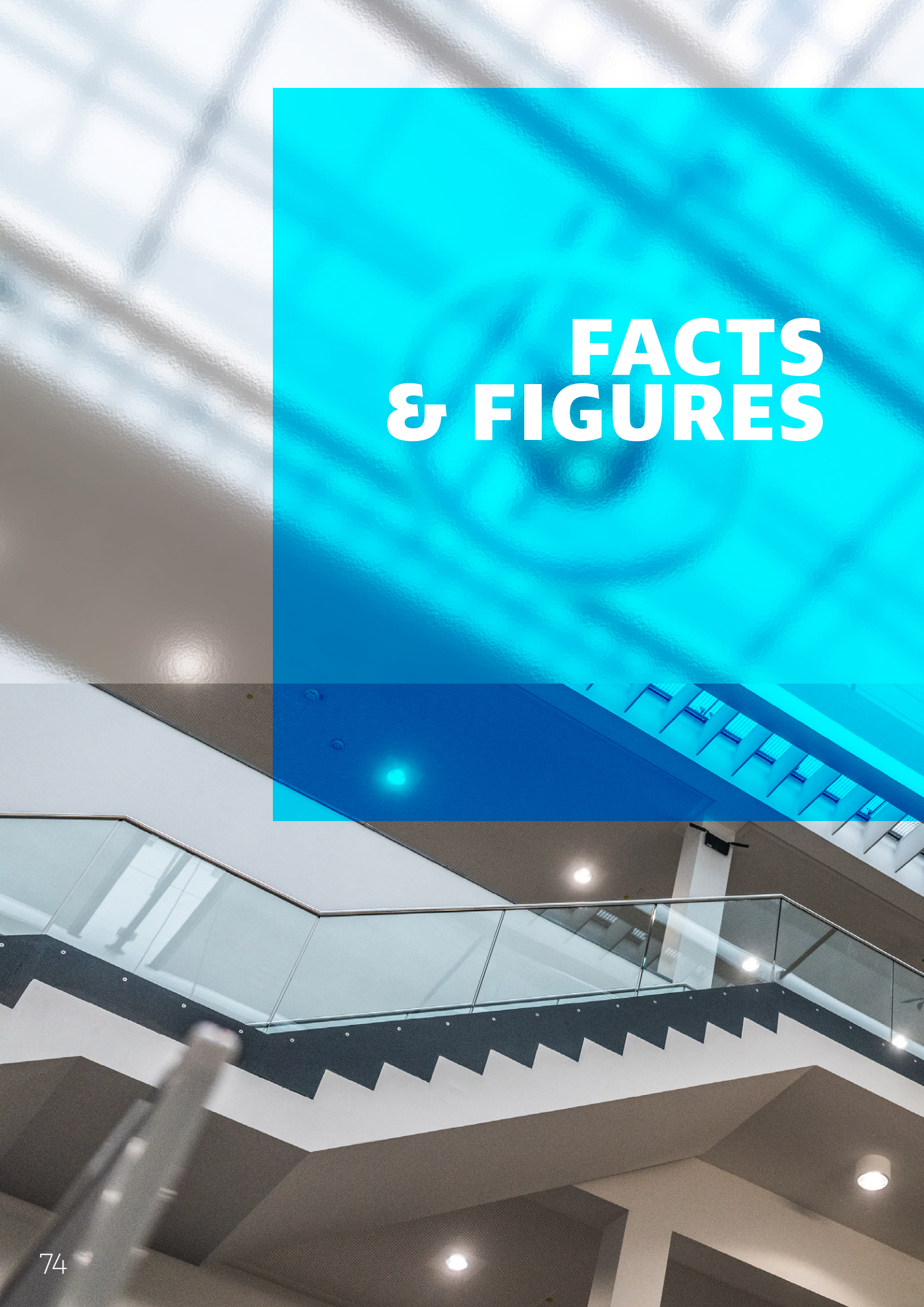
The Competence Hub for Spatial Transcriptomics brings together the expertise of the Microscopy, Genomics and Bioinformatics Core Facilities to enable advanced transcriptome analysis with spatial resolution. The centre aims to use the 10x Genomics CytAssist platform to provide spatial profiling of the entire transcriptome across whole tissue sections, including fixed and fresh-frozen samples. This will enable researchers to combine gene expression data with precise tissue architectures.



→ COMPETENCE HUB FOR BIOMEDICAL AI APPLICATIONS

Recently, IMB set up a Competence Hub for Biomedical AI Applications. This hub reflects the institute's strategic investment in forward-looking technologies such as AI and high-performance computing (HPC). It is intended to serve as a collaboration platform where experts from various disciplines can develop and implement AI-based tools for data-driven research. The Core Facilities operate dedicated server infrastructure for cutting-edge AI tools that enable advanced data analysis, interpretation and automation across a wide range of applications. For instance, an in-house developed, user-friendly AlphaFold infrastructure has been set up to help researchers efficiently predict protein structures and interactions. We also plan to develop customised, finely tuned LLM chatbots to provide accurate responses to frequently asked questions. The long-term goal is to create a comprehensive, AI-supported system to assist researchers.

FACTS & FIGURES



IMB Staff

No. staff nationalities
53

80%
European

20%
Rest of the world

No. employees by category

- **11** Master/Bachelor Students
- **79** PhD Students
- **37** Postdocs
- **43** Staff Scientists
- **26** Group Leaders
- **64** Technical staff
- **47** Admin & SciMan

Staff growth

2025: **307**

2020: **242**

2015: **229**

2010: **15**

No. scientific staff
198

55%
from abroad

45%
from Germany

Scientific Advisory Board

IMB is grateful to the members of our Scientific Advisory Board for the insight, guidance and advice that they have provided in order to help us continue to be a leading research centre.

Peter Becker (Chair)
Biomedical Center Munich, Ludwig Maximilian University (LMU), Munich, Germany

Marina Rodnina
Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

Bradley Cairns
Huntsman Cancer Institute, University of Utah, Salt Lake City, USA

Ruth Lehmann
The Whitehead Institute for Biomedical Research, Cambridge, USA

Special thanks to

Malene Hansen
Buck Institute for Research on Aging, Novato, USA

Andreas Ladurner
Ludwig Maximilian University (LMU), Munich, Germany

Ian Hickson
Center for Chromosome Stability & Center for Healthy Aging, University of Copenhagen, Denmark

Scientific Management

> We support our scientists so they can focus on their research.

IMB's Scientific Management assists our researchers across a wide range of areas, including:

- Communicating our researchers' achievements to the scientific community and public
- Support with organising scientific events at IMB
- Promoting social events to build a welcoming, collaborative atmosphere
- Organising seminars, training and career events
- Helping our researchers raise funding and manage their grants

Ralf Dahm
Director of Scientific Management

> We help our researchers organise events to hear about the latest developments, build collaborations & showcase their research.

IMB's public outreach & social media

- **Facebook** >9,700 followers
- **Bluesky** 467 followers
- **LinkedIn** 13,878

Communications & Events

- **25** seminars with national & international speakers per year
- **5** workshops & conferences per year
- Social events & alumni events

Science Writing

- **142** press releases since 2011
- Annual reports & IMB's website
- Institutional grant applications

> We write texts & produce videos to spread the news of our researchers' achievements.

3rd party funding in 2025:

€7.47 million

"We help our researchers obtain & manage extramural funding to advance their careers."

Fundraising & Grant Management

We manage IMB's extramural funding for:

- → **2** Collaborative Research Centres
- → **2** Research Training Groups
- **3** Innovative Training Networks
- → **10** ERC grants since 2011
  - ↳ **4** Advanced grants
  - ↳ **1** Consolidator grant
  - ↳ **4** Starting grants
  - ↳ **1** Proof of concept grant
- → **2** Heisenberg members
- **2** Emmy Noether group leaders

"We handle recruitment, training & finances for research initiatives to help them run smoothly."

Coordination of Research Initiatives

CRC 1361: Regulation of DNA Repair & Genome Stability

- → **22** Principal investigators
- → **13** PhD students & **10** postdocs
- → **€26.0M** (2019-2026)

4R RTG: R-Loop Regulation in Robustness & Resilience

- → **13** Principal investigators
- → **14** PhD students & **1** postdoc
- → **€8.7M** (2023-2027)

SHARP: Science of Healthy Ageing Research Programme

- → **25** Principal investigators
- → **11** PhD students
- → **€1.8M** (2021-2025)

RTG GenEvo: Gene Regulation in Evolution

- → **22** Principal investigators
- → **41** PhD students & **1** postdoc
- → **€14.1M** (2019-2028)

CoAGE: Cohorts for Healthy Ageing

- → **7** Principal investigators
- → **7** PhD students
- → **€1.3M** (2024-2027)

"We run training programmes for young researchers to help advance their careers."

Recruitment, Training & Career Development

- → Currently **37** postdocs & **202** PhD students, **214** PhD graduates since 2015
- → Career development events & mentoring programme
- → Hands-on training in scientific & professional skills

Extramural Funding in 2025

In addition to core funding from the Boehringer Ingelheim Foundation and the State of Rhineland-Palatinate, IMB is grateful for funding from the following:

Awards

CHRISTOPH CREMER
Emeritus Group Leader

David Glick Lectureship Award

AGATA IZABELA KALITA
PhD Student (Keller Valsecchi lab)

Elisabeth Gateff Prize 2025

CLAUDIA KELLER VALSECCHI
Group Leader

Friedrich Miescher Award 2025

RUXANDRA LAMBUTA
Postdoc (Papathanasiou lab)

EMBO Long-Term Fellowship

EDWARD LEMKE
Adjunct Director

Fellow of the Biophysical Society (USA) & Member of Academia Europaea

GABRIEL LONGO
PhD Student (Roukos lab)

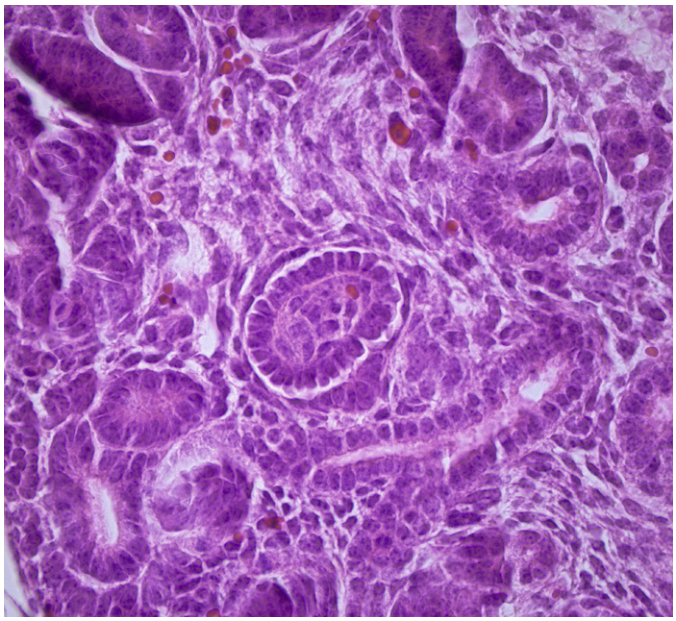
Walter Benjamin Fellowship

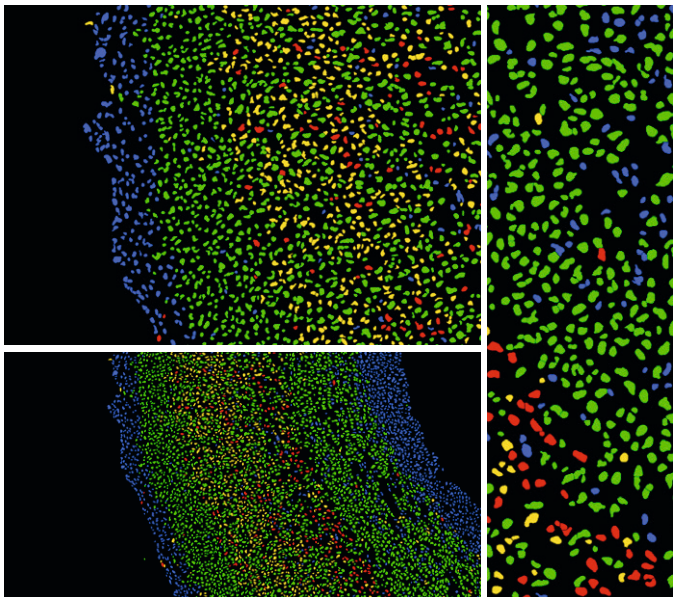
FEDERICO ULIANA
Postdoc (Dormann lab)

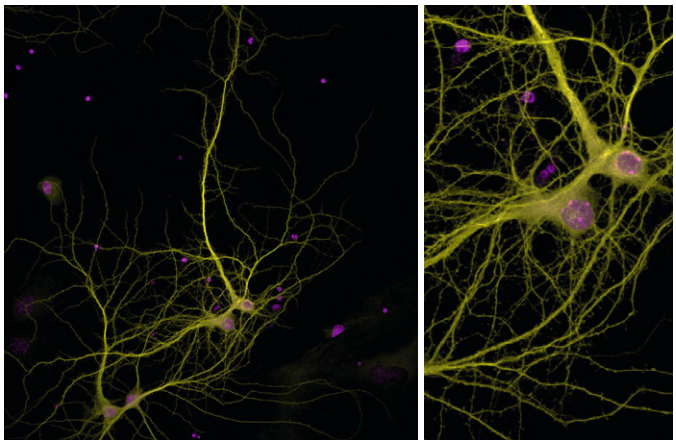
MSCA Postdoctoral Fellowship

SARA VIEIRA-SILVA
Adjunct Director

Highly Cited Researchers List, Clarivate Analytics (2022–2024)







Research & Training

We provide comprehensive training in scientific, technical and professional skills for students & postdocs, so they:

Learn from qualified professionals on how to give excellent presentations, write good papers, manage projects & lead a team

Connect with leaders from industry & academia at **career development events**

Join a vibrant & supportive community with **social events & annual retreats**

Master cutting-edge techniques & learn to use state-of-the-art scientific equipment with support from our Core Facilities experts

See our list of **training courses & lectures** on page 86–87 for more details.

> “I have enjoyed all of the journey, including all the **soft skills courses and the scientific training** that was provided to us and I am very much looking forward to applying these skills in my future career.”
>
> **Gaurav Joshi**, 2024 IPP Alumnus, Head of the Molecular Genetics Diagnostics Lab, Institute for Transfusion Medicine, University Medical Center Mainz

IMB Postdoc Programme (IPPro) & International PhD Programme (IPP)

IMB POSTDOC PROGRAMME

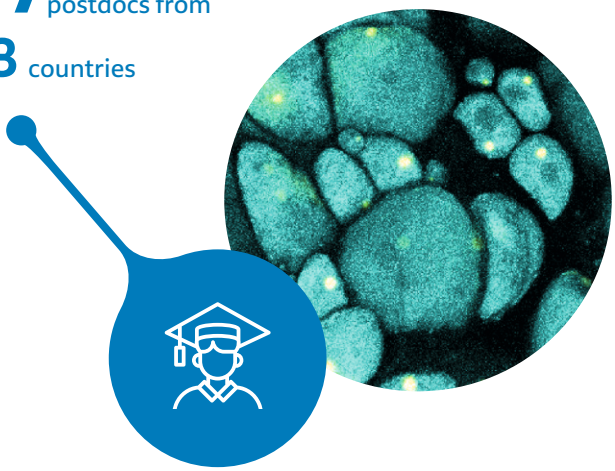
The **IMB Postdoc Programme (IPPro)** helps postdocs develop the skills and independence to manage their own projects and develop into scientific leaders.

It includes:

- **Guidance** from a supervisor and **mentoring** from leading scientists through the Mentoring Programme to support career development
- **Training** for higher-level scientists, including leadership, negotiation, grant writing and management skills
- Support in raising **funds** for becoming more independent

→ **www.imb.de/postdocs**

37 postdocs from
18 countries



INTERNATIONAL PHD PROGRAMME MAINZ

IMB's **International PhD Programme (IPP)** prepares PhD students for a successful scientific career through structured training and supervision so they can excel at tackling ambitious projects.

It includes:

- A broad and diverse **education** through lectures from leaders in the field, providing a solid foundation for a PhD project
- **Regular supervision** from 3 or more experts
- **Comprehensive training** in scientific, technical and professional skills to ensure they can succeed as a scientist

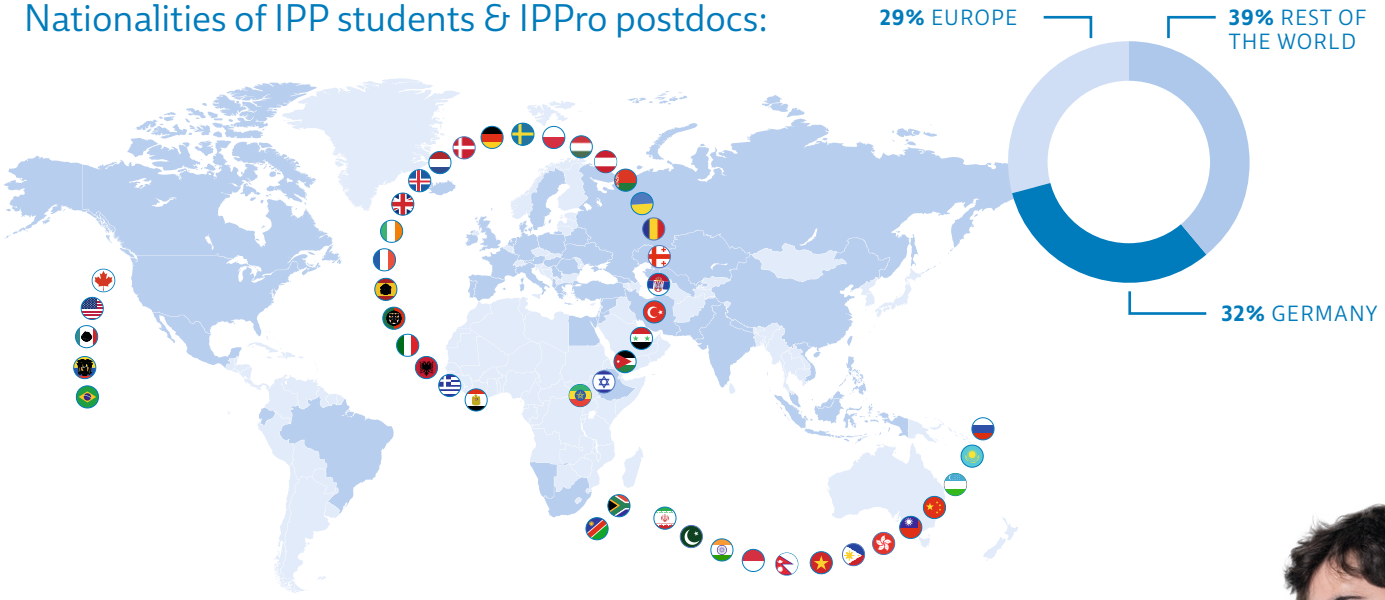
→ **www.imb.de/phd**

202 PhD students* from
41 countries in
76 research groups at IMB, Mainz University and its Medical Center
214 graduates since 2015

*of which 79 are at IMB

Research & Training

Nationalities of IPP students & IPPro postdocs:



Alumni from the IPP and IPPro work in industry, academia and beyond as:

- Professors
- Lab Heads
- Senior Research Scientists
- Managers
- Policy & Governance Officers
- Consultants
- Start-up Founders

369
IPP & IPPro publications in the last 5 years

76 publications in 2025

> "I loved the **vivid scientific and intercultural atmosphere** in the IPP. The array of scientific and soft skill courses **prepared me well for my next career steps** as a postdoc at the Babraham Institute in Cambridge and later when transitioning into industry."
>
> **Juri Kazakevych**, 2016 IPP Alumnus, Epigenomics Application Specialist, Diagenode

NextGen Training Programme (NexTPro)

NextGen TRAINING PROGRAMME

IMB's **NextGen Training Programme** is for undergraduate students from all over the world to gain experience working in the lab, including for work towards their thesis or an Erasmus placement. Placements can be from one month to a year.

Students can:

- → Work on their own project at the forefront of biological research
- → Get trained by leading experts in key scientific and transferable skills to give them a competitive edge in their studies
- → Gain comprehensive insights into the latest research through lectures from leading scientists to prepare them for Master's or PhD projects

→ **www.imb.de/nextpro**

> "The collaborative atmosphere, the **guidance** from highly skilled researchers, and the opportunity to contribute to **innovative scientific projects** have greatly enriched my academic journey. I am grateful for the supportive and friendly environment that has allowed me to grow both professionally and personally."
>
> **Yousef Al-Sha'ar**, Master's student 2024

> "The hands-on **training and mentorship** I received helped me grow both professionally and personally. IMB not only strengthened my research skills but also **gave me the confidence to pursue a future in science**."
>
> **Christina Chatzycrisou**, Erasmus fellow 2025

Training by our Core Facilities

IMB's Core Facilities offer lectures and hands-on courses to train researchers in key scientific techniques and a wide range of cutting-edge methodologies.

Courses are open to IMB researchers, students and affiliated staff (with some limited places for external researchers). Lectures are open to everyone.

LECTURES

GENERAL
- Molecular & biochemistry techniques

BIOINFORMATICS
- Databases in bioinformatics
- Design & analysis of NGS experiments
- AI methods and novel LMM tools in biomedical research

FLOW CYTOMETRY
- Flow cytometry: Introduction I
- Flow cytometry: Introduction II
- Flow cytometry overview (for MSc students)

GENOMICS
- Genomics (NGS)

MICROSCOPY & HISTOLOGY
- Introduction to microscopy
- Advanced microscopy techniques: From measuring mobility and interactions to super-resolution
- Histology & fluorescent labelling

PROTEIN PRODUCTION
- Protein production & crystallography

PROTEOMICS
- Proteomics

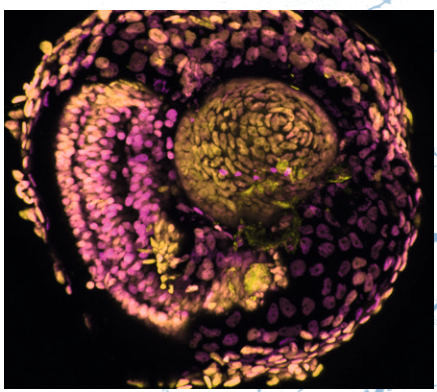
PRACTICAL COURSES

BIOINFORMATICS
- Introduction to biostatistics (6-day course, twice a year)
- Introduction to R (3-day course + one optional exercise session)
- Plotting with R (2-day course)
- Introduction to RNA-Seq analysis (2-day course)
- Introduction to ChIP-Seq and related NGS assays (2-day course)
- Data analysis using HPC and Nextflow (2-day course)

FLOW CYTOMETRY
- Basic flow cytometry practical course (2-day course)

MICROSCOPY
- Image processing & analysis (5-day course)
- Advanced hands-on microscopy: super-resolution (5-day course)
- Quantitative microscopy for (bio)polymers (CRC 1551) (5-day course)

PROTEOMICS
- Proteomics data analysis and practical course (2-day course)



Scientific & Transferable Skills Training

We provide our scientists with comprehensive training in both scientific and transferable skills to help them gain the expertise for top-quality research and success in their careers.

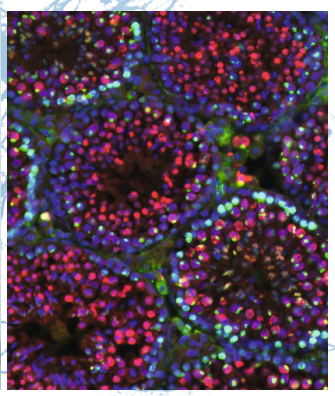
LECTURES

- CRC 1361 Master's module, including lecture series on "DNA Repair & Genome Stability"
- Data analysis with generative AI – potential & pitfalls
- Good scientific practice – protecting research integrity*
- How to manage & resolve conflict*
- Mental health in our communities
- Next-level productivity & quality in science using AI assistants*

PRACTICAL COURSES

- Adobe Illustrator for beginners (1-day course)
- Adobe Illustrator for intermediates (1-day course)
- Artifical intelligence as your research assistant (1-day course)
- Basics in science communication (1-day course)
- Building a strategic approach to research funding (1-day course)
- Critical reasoning & logic (2-day course)
- Mastering your PhD – project management for early-stage researchers (2-day course)*
- Research data management (half-day course)
- Scientific presentation skills (2-day course)
- Scientific writing (2-day course)
- Strategic career crafting (2-day course)
- Supervision & leadership (2-day course)
- Think before you write (scientific writing) (2-day course)*
- Using AI assistants to increase productivity (2-day course, organised by CRC 1361)

* Online lecture/course



Invited Speakers

IMB hosts regular talks with prestigious international leaders to promote networking and exchange of novel scientific ideas.

SCIENTIFIC SEMINARS

DATE	SEMINAR HOSTED BY	SPEAKER	AFFILIATION	TALK TITLE
06 Feb	IMB	**Stefano Piccolo**	University of Padua, IT	Cellular mechanotransduction in cancer and ageing
19 Feb	4R RTG & CRC 1361	**Nitika Taneja**	Erasmus University Medical Center, Rotterdam, NL	Mechanisms of chromatin reorganisation upon replication stress
13 Mar	CRC 1361	**Kristina Schmidt**	University of South Florida, Tampa, US	Unwinding the mechanism: the Bloom syndrome helicase and its role in genome stability
18 Mar	RTG GenEvo	**Estella Poloni**	University of Geneva, CH	Evolution of human genomic and phenotypic diversity linked to drug and dietary metabolisms
03 Apr	CRC 1361 students	**Jessica Downs**	The Institute of Cancer Research, London, UK	SWI/SNF chromatin remodelling, G quadruplexes, and genome stability
09 Apr	4R RTG	**David Monchaud**	University of Burgundy, Dijon, FR	Chemical biology-based approaches to modulate DNA/RNA secondary structures in human cells
21 May	4R RTG & CRC 1361	**Karlene Cimprich**	Stanford University School of Medicine, US	RNA meets DNA: dangerous liaisons in the genome
22 May	CRC 1361 students & 4R RTG	**Domenico Libri**	Institute of Molecular Genetics of Montpellier, FR	R-loops and the control of pervasive transcription revisited through the magnifying glass of CRAC
05 Jun	IMB Postdoc Programme	**Pedro Beltrao**	ETH Zurich, CH	Genetics of human trait variation - from protein structures to the organism
12 Jun	ReALity	**Chunaram Choudhary**	University of Copenhagen, DK	Acetylation, enhancers and gene regulation complexity
17 Jun	RTG GenEvo	**Nicholas Casewell**	Liverpool School of Tropical Medicine, UK	Causes and consequences of convergent evolution of defensive venom spitting in cobras
03 Jul	CRC 1361	**Haico von Attikum**	Leiden University Medical Center, NL	Unravelling DNA repair defects in human disease
09 Jul	4R RTG	**Frédéric Chédin**	University of California Davis, US	Mapping and imaging R-loops – a discussion about challenges and opportunities; co-transcriptional R-loops and their possible roles as genomic threats
16 Jul	4R RTG	**Damien D'Amours**	University of Ottawa, CA	The SMC5/6 complex: jumping through R-loops and other chromatin acrobatics
18 Sep	CRC 1361	**Rushad Pavri**	King's College London, UK	Regulation of somatic hypermutation by higher order chromatin structure
09 Oct	CRC 1361 & IMB Postdoc Programme	**Anna Poetsch**	Dresden University of Technology, DE	Does the genome encode its own stability?
16 Oct	CRC 1361	**Amir Aharoni**	Ben-Gurion University, Beer-Sheva, IL	Monitoring DNA damage and transcriptional bypass processes in live cells

11 Nov	RTG GenEvo	**Daniel Kronauer**	The Rockefeller University, New York, US	Differentiation, communication and collective behaviour in ant societies
13 Nov	CRC 1361, CRC 1551 & CHA	**Satpal Virdee**	University of Dundee, UK	Activity-based probes: unlocking hidden layers of the ubiquitin system
20 Nov	ReALity & IMB	**Adam Antebi**	Max Planck Institute for Biology of Ageing, Cologne, DE	Insights into resilience and restoration from fasting/refeeding and diapause
01 Dec	RTG GenEvo	**Viviana Barra**	University of Palermo, IT	Could DNA methylation change everything? Impact on chromosome stability, nuclear architecture and cell cycle
04 Dec	CRC 1361	**Niels Mailand**	University of Copenhagen, DK	Genome and epigenome maintenance by histone H1 family proteins
10 Dec	4R RTG & CRC 1361	**Massimo Lopes**	University of Zurich, CH	Replication fork plasticity in cancer and stem cells

TECHNICAL SEMINARS

DATE	SEMINAR HOSTED BY	SPEAKER	AFFILIATION	TALK TITLE
17 Apr	Core Facilities	**Lutz Priebe & Megha Bhardwaj**	Olink & DKFZ Heidelberg, DE	Advance biomarker discovery and clinical research with PEA™ technology: Unlocking the future: next-generation proteomics with Olink – advancing diagnostics and therapeutics
17 Apr	Core Facilities	**Lutz Priebe & Megha Bhardwaj**	Olink & DKFZ Heidelberg, DE	Advance biomarker discovery and clinical research with PEA™ technology: Blood proteome and cancer
17 Sep	Scientific Management	**Nancie Mooney**	Thermo Fisher Scientific, DE	Tips and tricks for advanced multiplexed IHC workflows for enhanced spatial phenotyping
14 Oct	Core Facilities	**Ilias Zarguit**	1NA, Leiden, NL	High-throughput single-molecule analysis of DNA-protein interactions using DNA curtains
28 Oct	Scientific Management	**Kris Künemund**	BMKGENE Biomarker Technologies, DE	Spatial transcriptomics
24 Nov	Core Facilities	**Selina Woeste**	10x Genomics, Leiden, NL	From tissue to transcript: discover visium spatial technology

Research Initiatives

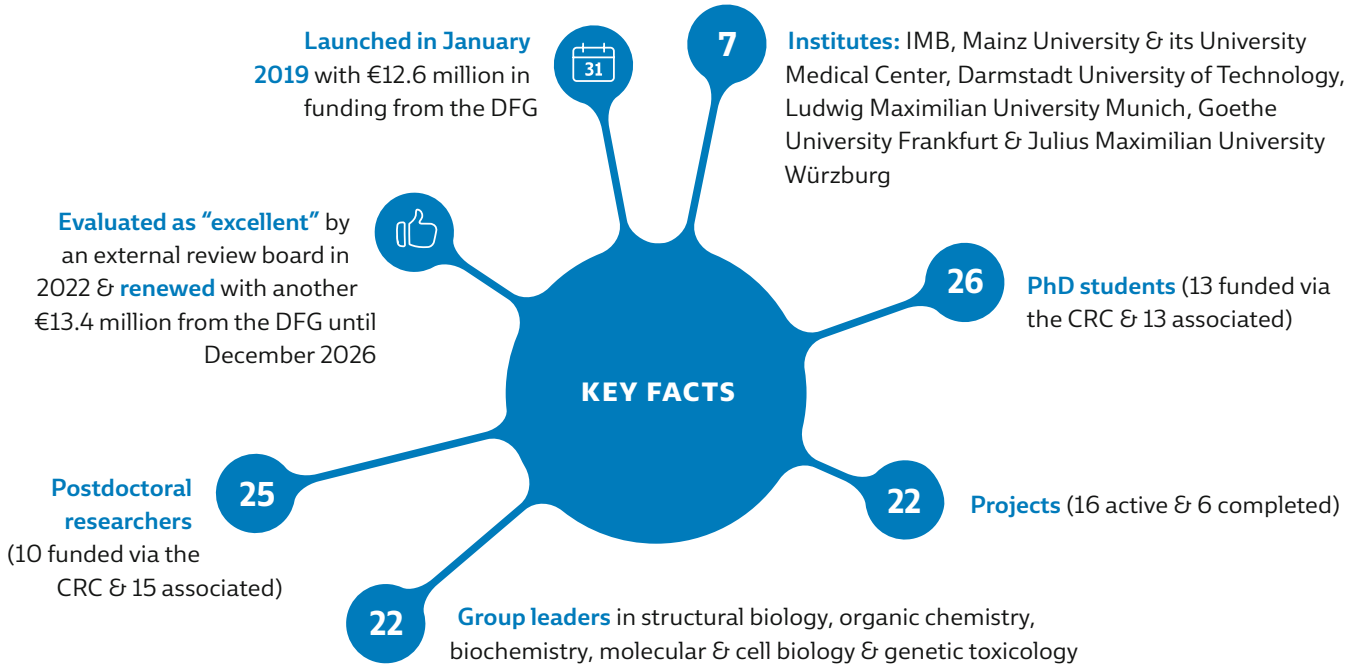
CRC 1361 "Regulation of DNA Repair & Genome Stability"

Spokesperson: Helle Ulrich

The Collaborative Research Centre (CRC) 1361 seeks to elucidate the regulatory mechanisms governing the choice between individual genome maintenance pathways and their fidelity, interdependencies and contributions to cellular physiology.

CRC 1361 group leaders at a Korea-EU Collaborative Research Project kick-off symposium in 2025


2025 Annual Retreat of the CRC 1361



In 2025, CRC 1361 researchers published 25 papers from projects funded by this initiative. Our retreat took place at Himmelspforten in Würzburg over 3 days, with intense rounds of discussions and idea pitches to plan for the CRC's upcoming evaluation and third funding period. Members also took a guided tour through the Würzburg Residence.

In conjunction with International Women's Day, the CRC 1361 banded together with the CRC 1551, 4R RTG, and GenEvo RTG to organise a full-day "Bright Future Meeting" for participating female PhD students and postdocs. The event started with a workshop on "Business with Attention", followed by an all-female career panel with panellists who shared their vast experiences from diverse professions and backgrounds.

→ **www.sfb1361.de**

CRC 1551 "Polymer Concepts in Cellular Function"

Spokesperson: Edward Lemke, Vice-Spokesperson: Dorothee Dormann

The Collaborative Research Centre (CRC) 1551 brings together polymer and life scientists to understand the dynamic interplay between different biopolymers and how they govern cellular function.

Joint CRC 1551 and SPP 2191 retreat

CRC 1551 at the 2025 Mainz Carnival Parade

2025 Annual Retreat of the CRC 1551

KEY FACTS

Launched in January 2023 with €12.3 million from the DFG

16 **Interdisciplinary projects & 4 service projects** in transcription, protein aggregation, proteostasis & the formation of higher-order complexes & membraneless organelles

37 **Group leaders**, as well as 11 associate group leaders

4 **Main institutes:** Mainz University, its University Medical Center, IMB, the Max Planck Institute for Polymer Research & 3 satellites (the Max Planck Institute for Biophysics, University of Stuttgart & University of Würzburg)

In 2025, the CRC 1551 received DFG approval for two new projects on "Covalent and non-covalent macromolecular approaches for precision and switchable protein oligomerization: exploring fundamental insights and controlling cellular functions", led by Shikha Dhiman (Mainz University), and "Nucleation dynamics in field theories for intracellular phase separation", led by Michael te Vrugt (Mainz University).

A notable highlight was the CRC's participation in the Mainz Carnival parade, a major outreach event attended by 600,000 people and broadcast live on national TV. The CRC also held its annual retreat in Mainz, which brought together 100 members and the newly-appointed external Scientific Advisory Board for a vibrant scientific exchange.

Educational activities included a joint student and postdoc retreat with the SPP2191 network on "Molecular mechanisms of functional phase separation" in Bonn, the second iteration of the Master's Module on "Polymer concepts in cellular function", and a mentoring programme for PhD students.

→ **https://crc1551.com**

RTG GenEvo: "Gene Regulation in Evolution"

Spokespersons: Susanne Foitzik (JGU) & René Ketting (IMB)

GenEvo RESEARCH TRAINING GROUP

GenEvo centres on the core question of how complex and multi-layered gene regulatory systems have both evolved and driven evolution. The initiative trains PhD students to work at the interface of these two themes while receiving a broad, interdisciplinary education.

This Research Training Group (RTG) is a collaboration between Mainz University's Faculty of Biology and IMB.

2025 GenEvo Student Retreat

Group leaders at the 2025 GenEvo PI retreat

14 **Interdisciplinary projects** fusing evolutionary & molecular biology

Launched in June 2019 with €6.7 million in funding from the DFG

GenEvo Symposium attendees

KEY FACTS

Positively evaluated in 2023 & approved for a second funding period with an additional €7.4 million from the DFG until 2028

22 **Group leaders** (plus 8 contributing group leaders), one postdoc & 41 PhD students (plus 22 associated PhD students)

GenEvo students have been authors on 34 papers, including in *iScience*, *Molecular Cell* and *Nature Communications*. In 2025, four associated GenEvo students successfully defended their theses (making 11 GenEvo graduates and 7 associated GenEvo graduates in total) and two new IMB group leaders joined (Jan Padeken and Katharina Papsdorf). Notable events included the GenEvo symposium in March for GenEvo students from different cohorts to network, the GenEvo student retreat in Karlsruhe in July, and the GenEvo PI retreat in Guntersblum in October.

→ **www.genevo-rtg.de**

Science of Healthy Ageing Research Programme (SHARP)

This joint PhD training programme combines the complementary skills of basic and clinical/translational researchers to gain new insights into the underlying causes of ageing and discover new ways to prevent age-related diseases. SHARP brings together researchers from IMB, Johannes Gutenberg University Mainz and its University Medical Center to work on projects focusing on ageing and longevity. As of 2025, 13 papers have been published from this programme.

Launched in 2021 with €1.8 million in funding from Rhineland-Palatinate's Ministry of Science & Health

KEY FACTS

- **25** Group leaders
- **14** **Projects** covering stem cell biology, epidemiology, immunology, cardiology, neurobiology, cancer biology, epigenetics, proteomics, telomere biology, RNA biology, DNA repair & autophagy
- **11** PhD students

2nd CHA Workshop 2025 for researchers working on ageing (including SHARP members)

→ **www.cha-mainz.de/sharp**

CHA Programme for Clinician Scientists (CHANCE)

CHANCE strengthens translational ageing research within the framework of the Centre for Healthy Ageing (CHA) by fostering collaborations between IMB, Johannes Gutenberg University Mainz and its University Medical Center on key research topics in ageing and age-related diseases.

2nd CHA Workshop 2025

KEY FACTS

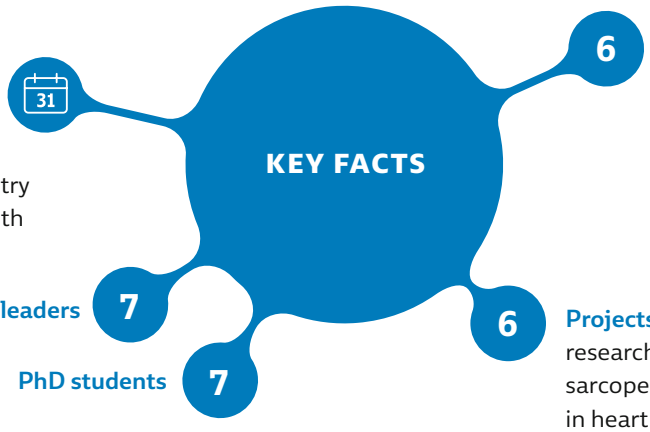
- **3** **Institutes:** IMB, Mainz University & its University Medical Center
- **5** Clinician Scientists & Advanced Clinician Scientists
- **Launched in 2023** & funded with €1.2 million by Rhineland-Palatinate's Ministry of Science & Health

→ **www.cha-mainz.de/chance**

Cohorts for Healthy Ageing (CoAGE)

CoAGE brings together seven experts in healthy ageing and age-related diseases from across Germany to address current issues in an interdisciplinary manner. Each expert leads a major cohort study and supervises a PhD student in an ageing-related project. The findings will provide valuable insights into the causes of disease and healthy ageing. As of 2025, one paper has been published from this programme.

Launched in 2024 & funded with €1.3 million by Rhineland-Palatinate's Ministry of Science & Health



Institutes: Helmholtz Centre Munich, German Center for Neurodegenerative Diseases (DZNE) Bonn, University Medical Center Hamburg-Eppendorf, Leipzig University, Greifswald University Hospital, & University Medical Center Mainz

Group leaders

PhD students

Projects covering different aspects of epidemiological research, including cardiometabolic multimorbidity, sarcopenia, organic ageing clocks, biomarker research in heart failure, sexual dimorphism in lipid metabolism, thrombotic diseases & COVID-19 population research

→ **www.cha-mainz.de/coage**

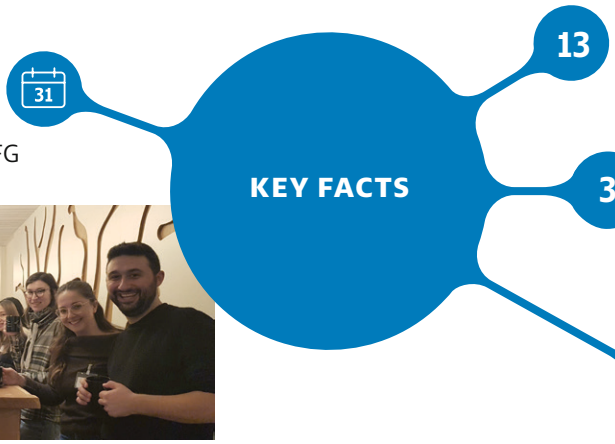
4R RTG: "R-loop Regulation in Robustness & Resilience (4R)"

Spokespersons: Brian Luke & René Ketting

The Research Training Group (RTG) 4R delves into the impact of R-loops on the orchestration of complex cellular processes that promote robustness and resilience. The biological processes being comprehensively explored include DNA repair, telomere maintenance, transcription-replication conflicts, gene regulation and RNA processing.

R-loop Regulation in Robustness & Resilience

Launched in 2023 with €8.7 million in funding from the DFG



Group leaders, 14 PhD students & one bioinformatics postdoc, as well as five associated members

Institutes: IMB, Mainz University & its University Medical Center

Projects


Members of 4R at the mid-term retreat

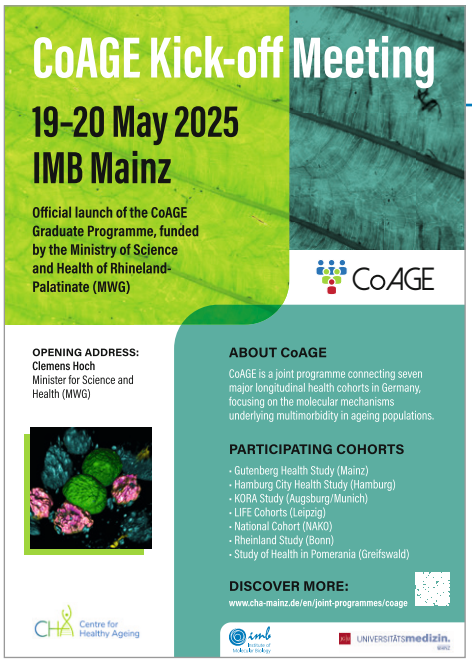
In 2025, 4R continued to expand by welcoming two new IMB groups (Sina Wittmann and Siyao Wang) and recruiting eight new PhD students. 4R group leaders Julian König, Maria Felicia Basilicata, and Claudia Keller Valsecchi received professorships outside Mainz University and left 4R – we sincerely congratulate them on their great success!

The 4R mid-term retreat was held in Geisenheim in November. This event focused on both scientific collaboration and strengthening the bonds between our two student cohorts. Additionally, 4R hosted 12 seminar speakers throughout the year, including five joint events with the CRC 1361.

→ **4r-rtg.de**

Scientific Events

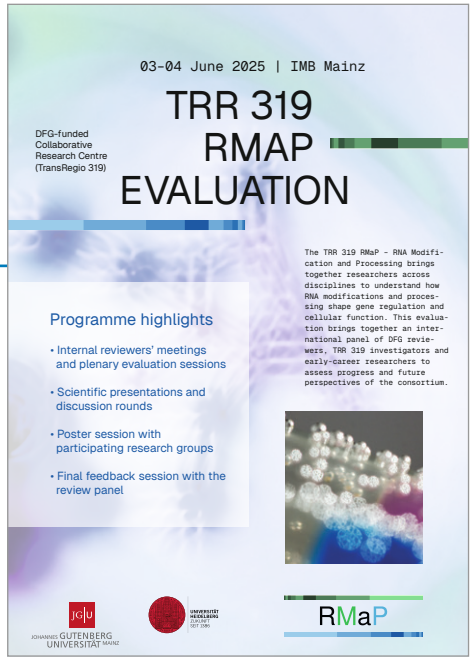
Scientific events organised by IMB in 2025:



19-20 MAY

Cohorts for Healthy Ageing (CoAGE) Kick-off Meeting

Scientific organisers:
Christof Niehrs (IMB),
Philipp Wild (IMB/University Medical Center Mainz)



03-04 JUNE

Transregio TRR 319 RNA Modification and Processing (RMaP) Evaluation

Scientific organisers:
Mark Helm (Mainz University)

26 JUNE

2nd Life Sciences Postdoc Symposium Mainz

Scientific organisers:
Representatives of the IMB Postdoc Programme

13 NOVEMBER

Centre for Healthy Ageing (CHA) Workshop

Scientific organisers:
Peter Baumann (IMB/Mainz University),
Christof Niehrs (IMB)

Publications

BAUMANN

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Hough SH*, Jhujh SS*, Awwad SW*, Lewis OE*, Lam S, Thomas JC, Mosler T, Bader A, Bartik L, McKee S, Amudhavalli S, Colin E, Damseh N, Clement E, Cacheiro P, Majumdar A, Smedley D, Fluss J, Giannini R, Thiffault I, Zagnoli Vieira G, Belotserkovskaya R, Smerdon SJ, Beli P, Galanty Y, Carnie CJ, Stewart GS and Jackson SP (2025) Loss of CTLH component MAEA impairs DNA repair and replication and leads to developmental delay. *EMBO Mol Med*, doi: 10.1038/s44321-025-00352-x

Longo GMC*, Sayols S*, Kotini AG, Heinen S, Möckel MM, Beli P and Roukos V (2025) Linking CRISPR-Cas9 double-strand break profiles to gene editing precision with BreakTag. *Nat Biotechnol*, 43:608–622

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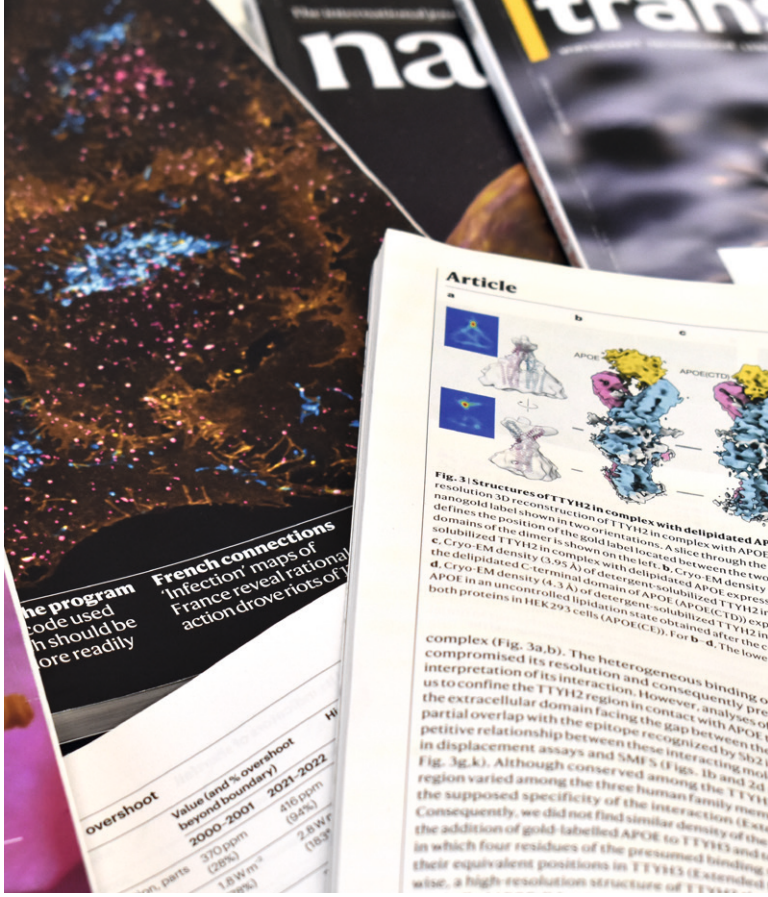

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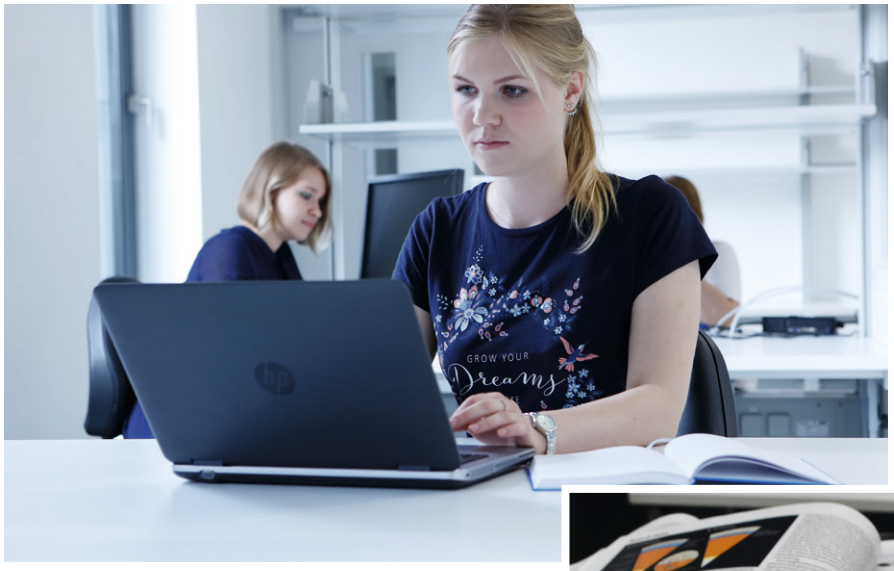

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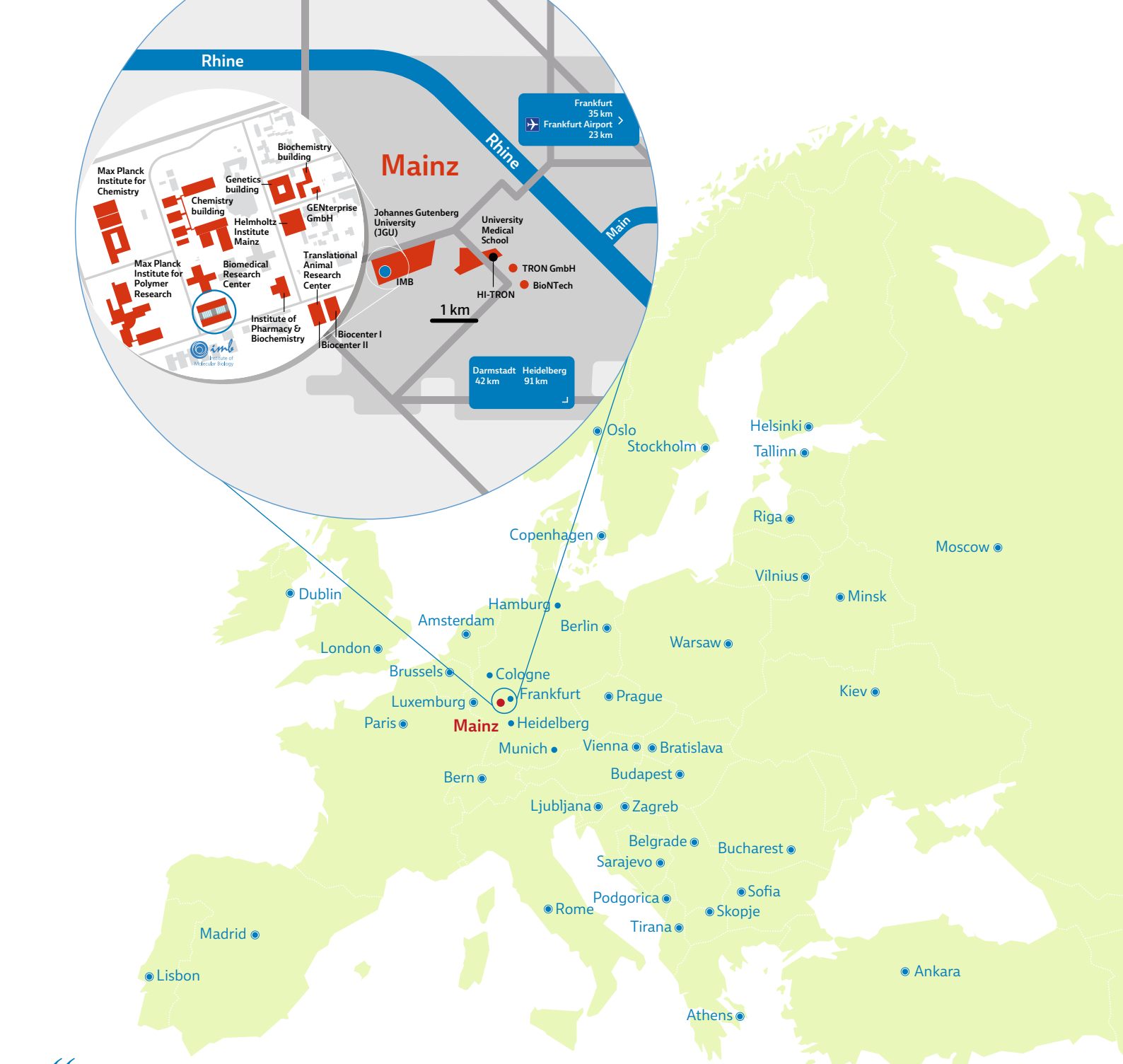
* indicates joint contribution, # indicates joint correspondence, ° indicates joint senior authorship



“Mainz has a very international research community that opens plenty of doors for job opportunities and life experiences.”

- Chiara Galante, IPP Alumna

Research Environment

IMB is embedded in a strong and dynamic research environment on the campus of Johannes Gutenberg University, just west of Mainz city centre.

With 10 departments, more than 150 institutes and 32,000 students, Johannes Gutenberg University is one of the largest German universities. The university has strong, interdisciplinary centres dedicated to neuroscience, cardiovascular medicine, immunology and oncology.

IMB also has strong collaborative links to the **University Medical Center**, which is located near the main campus and has a strong focus on clinical and translational research. The **Max Planck Institute for Chemistry**, **Max Planck Institute for Polymer Research**, **Leibniz Institute for Resilience Research** and **Mainz's University of Applied Sciences** are also all within easy reach.

Frankfurt, only 35 km away, is home to **Goethe University**, with over 46,000 students. Research institutes in Frankfurt include the **Max Planck Institute for Biophysics**, **the Max Planck Institute for Brain Research** and the **Ernst Strungmann Institute for Cognitive Brain Research.**

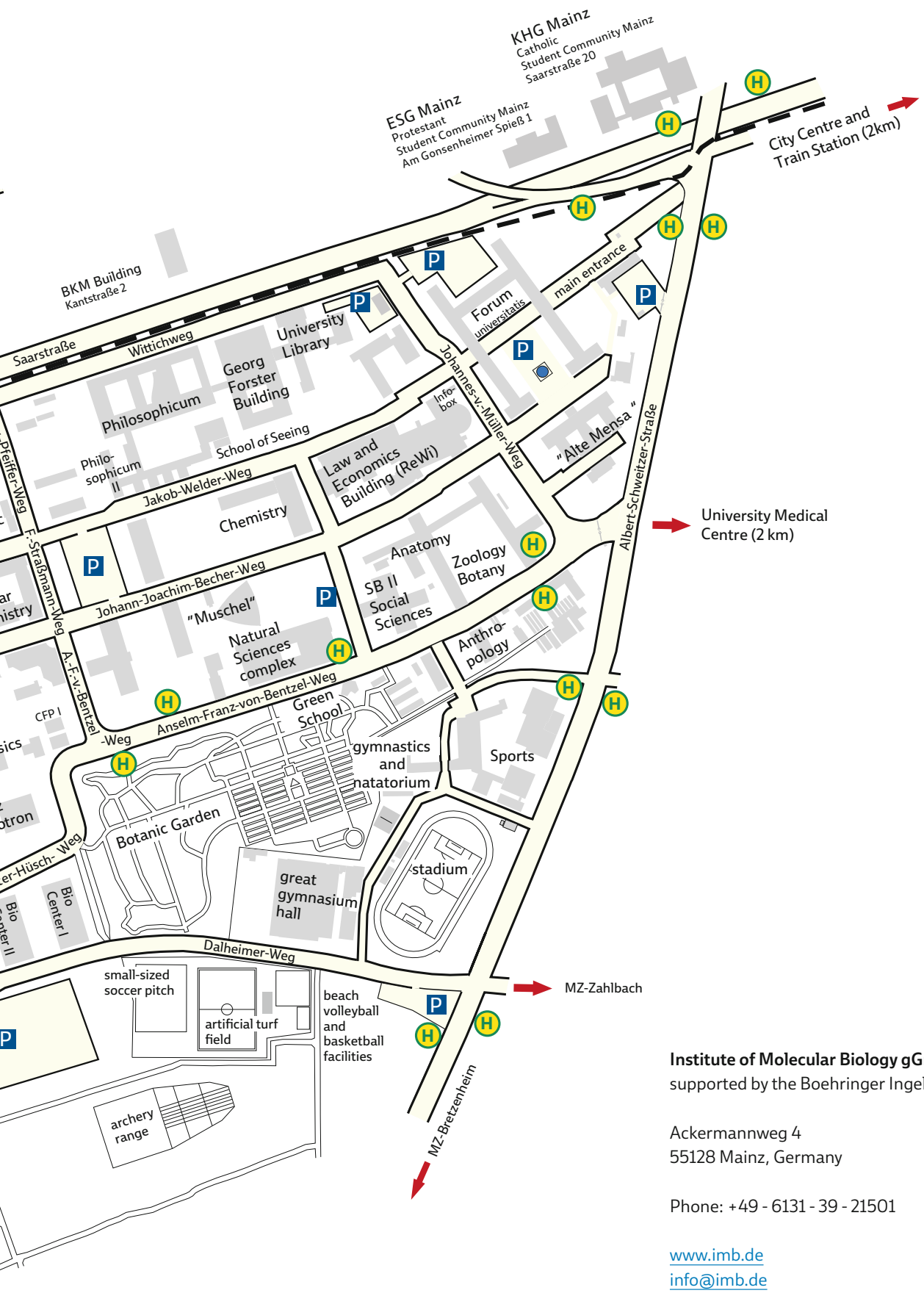
Nearby, Darmstadt is home to both a **Technical University**, whose Department of Biology has a focus on synthetic biology and the biology of stress responses, and a **University of Applied Sciences** which includes a focus on biotechnology.

There is an **extensive industry R&D** presence in Mainz, with the headquarters of **Boehringer Ingelheim**, **BioNTech**, **Translational Oncology (TRON)** and the **Merck Group** in close vicinity.

WHERE WE ARE

Mainz is a charming, open-minded city that dates back 2,000 years to Roman times and still has a historic centre with a magnificent medieval cathedral. It was here, in 1450, that Johannes Gutenberg invented modern book printing. The city is located at the confluence of two of the most important rivers in Germany, the Rhine and the Main, and has spectacular esplanades. Mainz is within easy reach of both cosmopolitan Frankfurt, with its famous opera house, avant-garde museums and glass-and-steel banking district, and the Rhine valley region with its castles, vineyards and nature reserves that offer great outdoor activities. With Frankfurt airport – one of the largest airports in Europe – only 25 minutes away, countless destinations are within easy reach.

Campus Map & Contact



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Cover: DNA repair in yeast cells. DNA repair activity is labelled in green, the nuclear periphery is indicated in red, and an unrelated repair compartment at the nuclear periphery in blue. Image credit: Ronald Wong (Ulrich group).
Inner cover: Tracking the movement patterns of a *C. elegans* population over time. Image credit: Jan Padeken.
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(p5) Lipid droplets (green) and mitochondria (magenta) in young adult *C. elegans* intestinal cells. Image credit: Sebastian Steinmüller (Papsdorf group).
(p6-7) Giemsa staining of bone epiphyses from Scurfy mice (FoxP3+ Treg depletion). Image credit: Mia de Haas (Guezguez group, UMC).
(p52-53) False-coloured fluorescence image showing midgut caeca of the grain weevil *Sitphilus oryzae*, stained for nuclei (cyan), *Sodalis pierantonius* endosymbionts (yellow) and wheat germ agglutinin (magenta). Image credit: Petri Turunen (Microscopy Core Facility) & Tobias Engl (Institute of Organismic and Molecular Evolution, JGU).
(p81) Top: H&E staining of a cholangiocarcinoma in mouse liver. Middle: Cell phenotype detection and cortical distance with machine learning in mouse brains. Image credit: Jennifer Sitta (Lutz group, UMC) & Petri Turunen (Microscopy Core Facility). Bottom: Confocal fluorescence image of mouse hippocampal neurons. Image credit: Bilal Akhtar (Niehrs group).
(p83) Balbiani bodies in a zebrafish oocyte. Image credit: Alessandro Consorte (Ketting group).
(p86) *Xenopus* embryo eye. Image credit: Victoria Hatch (Niehrs group).
(p87) Immunofluorescence image of a mouse testis cross-section showing complete spermatogenesis. DNA is labelled in blue (DAPI), germ cells are shown in red (GCNA), and spermatogonial stem cells in green (PLZF). Image credit: Joan Barau.
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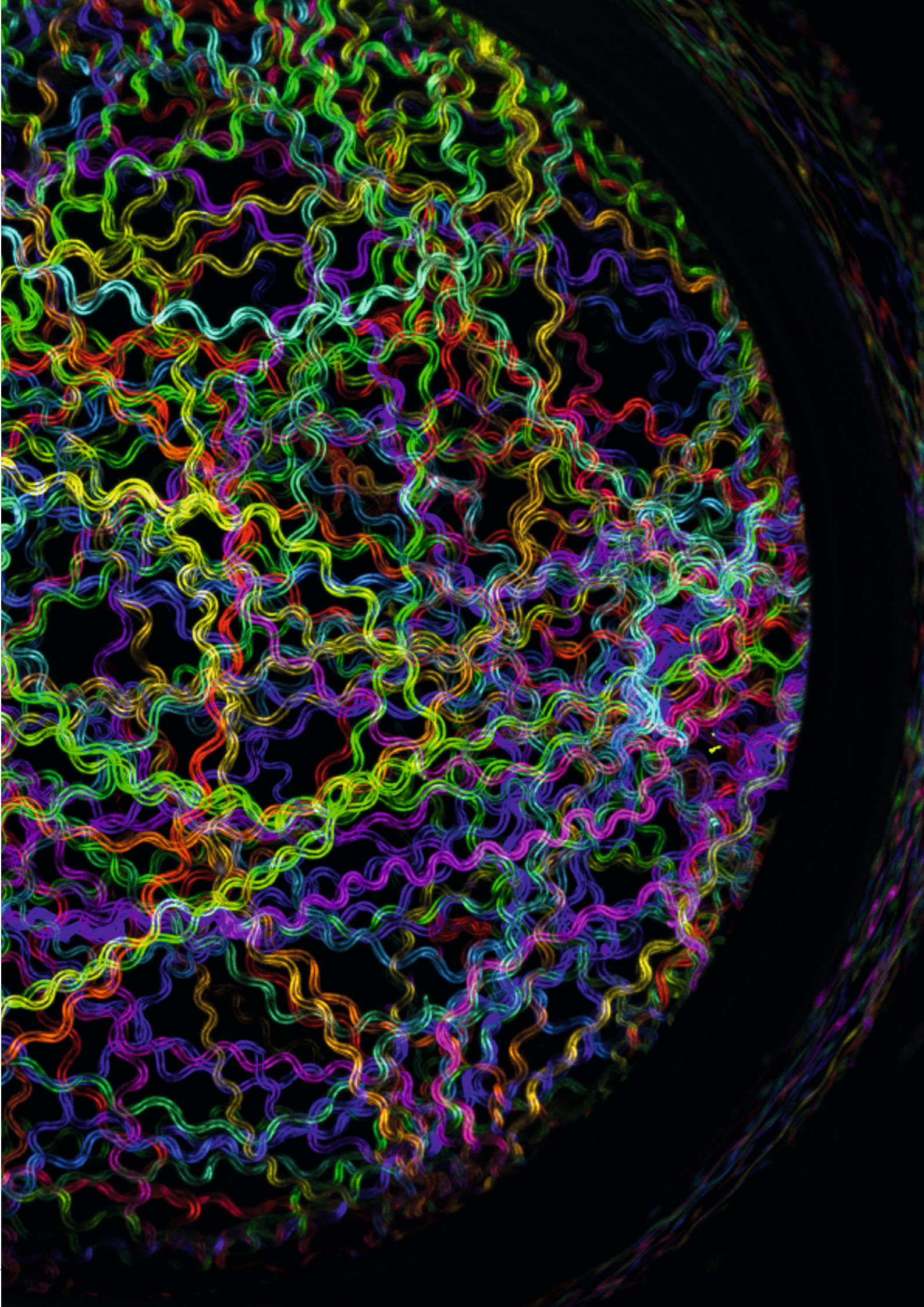

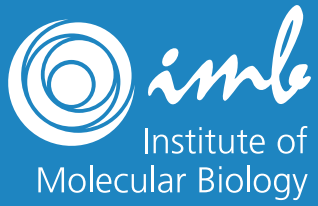
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